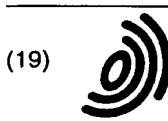


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(11) **EP 0 579 496 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention  
of the grant of the patent:  
**14.11.2001 Bulletin 2001/46**

(51) Int Cl.<sup>7</sup>: **C07D 401/04, C07D 401/06,  
C07D 405/04, C07D 409/04,  
C07D 413/14, C07D 401/14,  
C07D 409/14, A61K 31/505**

(21) Application number: **93305557.6**

(22) Date of filing: **15.07.1993**

(54) **4-Aminoquinazoline derivatives, and their use as medicine**

4-Aminochinazolin-Derivate, deren Verwendung als Heilmittel

Dérivés de 4-aminoquinazolines, leur utilisation comme médicaments

(84) Designated Contracting States:  
**AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL  
PT SE**

(30) Priority: **15.07.1992 US 913473  
14.06.1993 US 76431**

(43) Date of publication of application:  
**19.01.1994 Bulletin 1994/03**

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**FR-A- 2 102 221 FR-A- 2 310 756**  
**GB-A- 2 002 746**

Remarks:

The file contains technical information submitted  
after the application was filed and not included in this  
specification

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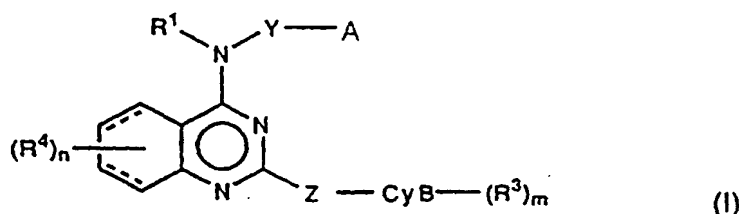
EP 0 579 496 B1

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## Description

[0001] The present invention relates to novel 4-aminoquinazoline derivatives. More particularly, this invention relates to:

(i) 4-aminoquinazoline derivatives of the following formula:



wherein all of the symbols have the same meanings as described hereinafter, and the pharmaceutically acceptable acid addition salts thereof, the pharmaceutically acceptable salts thereof, and the hydrates thereof, which have inhibitory activity on cyclic guanosine 3',5'-monophosphate phosphodiesterase, or additionally on thromboxane  $A_2$  synthetase,

(ii) processes for the preparation thereof,

(iii) inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterase, or additionally of thromboxane  $A_2$  synthetase containing them, and

(iv) methods of prophylactic and curative treatment of mammals, including humans, by administering an effective amount of the compounds of the formula (I), the pharmaceutically acceptable acid addition salts thereof, the pharmaceutically acceptable salts thereof, and the hydrates thereof, to the patient to be treated.

[0002] Cyclic guanosine 3',5'-monophosphate (abbreviated as cGMP hereafter) was found in urine in rats by D. F. Ashman in 1963. Till now, it has been known that cGMP is distributed broadly in tissues of any animals including human beings. cGMP is biosynthesized from guanosine triphosphate (GTP) by the action of guanylate cyclase.

[0003] cGMP has been experimentally confirmed to have various physiological activities. For example, cGMP induces the relaxation of heart muscle and of smooth muscle. Further, it is related to the formation of neuronal synapses, and it acts as a trigger of cell proliferation and it induces the proliferation of lymphocyte.

[0004] cGMP is metabolized to physiologically inactive 5'-GMP by the action of cGMP phosphodiesterase (abbreviated as cGMP-PDE hereafter).

[0005] Accordingly, the inhibition of the action of cGMP-PDE is considered to be useful for the prevention and/or treatment of diseases induced by enhancement of the metabolism of cGMP, such as hypertension, heart failure, myocardial infarction, angina, atherosclerosis, cardiac edema, pulmonary hypertension, renal insufficiency, nephrotic edema, hepatic edema, asthma, bronchitis, dementia, immunodeficiency.

[0006] On the other hand, thromboxane  $A_2$  (abbreviated as  $TXA_2$  hereafter) was found as a constituent of the arachidonate cascade, in platelets by M. Hamberg in 1975.  $TXA_2$  is biosynthesized from arachidonic acid released from cell membrane via prostaglandin  $G_2$  and prostaglandin  $H_2$ , and rapidly metabolized to inactive thromboxane  $B_2$ .  $TXA_2$  is known to induce platelet aggregation and to contract smooth muscle, particularly blood vessel muscle and bronchial muscle.  $TXA_2$  synthetase was isolated and purified from microsome in platelets.

[0007] Accordingly, the inhibition of  $TXA_2$  synthetase decreases the biosynthesis of  $TXA_2$ , and is useful for the prevention and/or treatment of inflammation, hypertension, thrombosis, arteriosclerosis, cerebral apoplexy, asthma, myocardial infarction, cardiostenosis, cerebral infarction, etc.

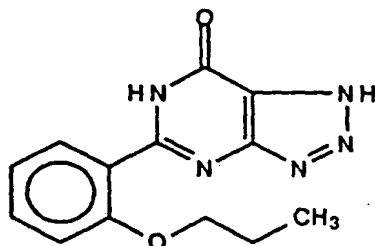
[0008] It is considered that almost any disease occurs by the complex interaction of plural mechanisms. Accordingly, the inhibition of any one of the plural mechanism is not adequate to treat a disease. A medicament inhibiting as many mechanisms as possible, which induce the disease, is considered to be effective and ideal.

[0009] Especially, it is very useful for the prevention and/or treatment of diseases induced by platelet aggregation, e.g. angina pectoris, heart failure, pulmonary hypertension and various kinds of renal diseases to have inhibitory active on both cGMP PDE and  $TXA_2$  synthetase.

## Related Arts

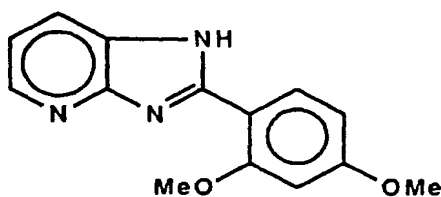
[0010] Up to now, some compounds have been known as cGMP-PDE inhibitors, for example,

## Zaprinast



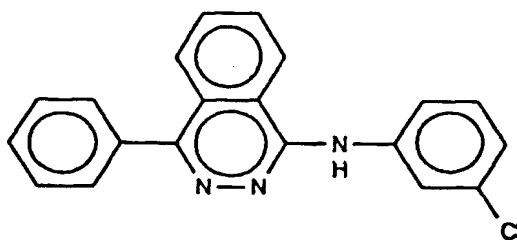
(A)

## AR-L 57



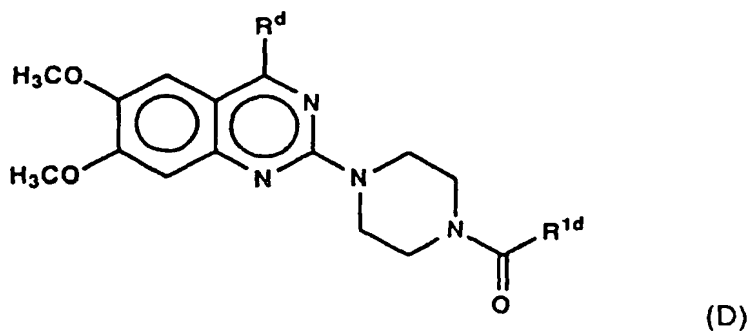
(B)

## MY-5445



(C)

[0011] Many compounds derived from the above lead compounds have been proposed and many patent applications relating to those have been filed. For example, as derivatives of Zaprinast, compounds wherein the 1 H-1,2,3-triazole skeleton is replaced by various other hetero cycles (see USP-5047404), those wherein the triazole is replaced by a benzene ring (see EP-371731), and those wherein the triazole is eliminated, i.e. those having only the pyrimidine skeleton (see EP-395328), have been proposed. The above mentioned compounds always contain an oxo group at the 4th position of the pyrimidine skeleton. The compounds having an amino group at the said position are described in USP-4060615. The specification discloses 4-amino-6,7-dimethoxy-2-piperazinyquinazoline derivatives of the following formula:

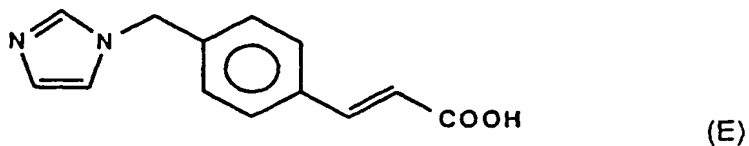


wherein  $R^d$  is amino or hydrazino,

$R^{1d}$  is C3-8 cycloalkyl, C3-8 methylcycloalkyl or C4-8 cycloalkenyl, and their acid addition salts.

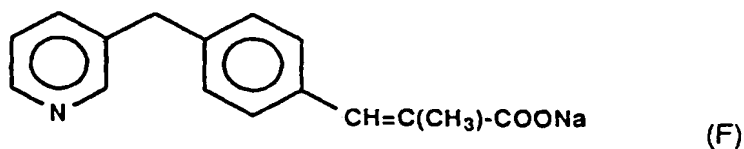
[0012] Furthermore, some  $TXA_2$  synthetase inhibitors have been known, for example,

OKY-046



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ONO-1581

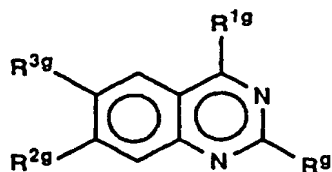


[0013] Many derivatives containing an imidazole or pyridine ring as the basic skeleton have been proposed. However, there appears to be no  $TXA_2$  synthetase inhibitor having both the said ring and quinazoline ring.

[0014] On the other hand, many compounds having a quinazoline ring as the skeleton, which are not known to have inhibitory activity on cGMP-PDE and/or on  $TXA_2$  synthetase, have been proposed.

[0015] For example, as to 4-aminoquinazoline derivatives having cyclic groups at the 2nd position thereof and as N-substituent,

(1) USP-3772295 discloses the compounds of the formula:



(G)

wherein

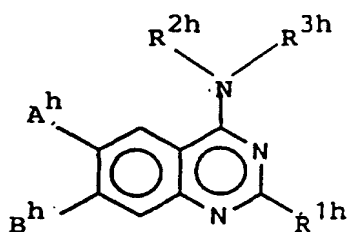
R<sup>1g</sup> is cyclopentylamino, trifluoromethylanilino, furfurylamino, 3-furylmethylamino, tetrahydrofurfurylamino or tetrahydro-3-furylmethylamino etc;

R<sup>g</sup> is hydrogen, phenyl substituted by one or more methyl, methoxy, chlorine, fluorine or methylenedioxy, a residue derived from furan, thiophene, pyridine, picoline, benzofuran or benzothiophene, or naphthyl;

R<sup>2g</sup> and R<sup>3g</sup> are hydrogen or chlorine;

and their acid addition salts, being useful as diuretics,

(2) GBP-1199768 discloses the compounds of the formula:



(H)

wherein

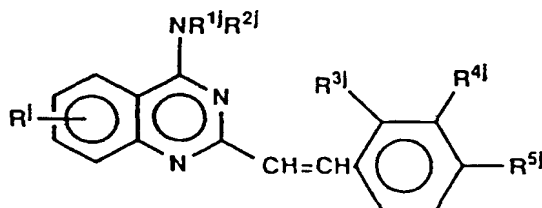
each A<sup>h</sup> and B<sup>h</sup> are C1-5 alkoxy, hydrogen, hydroxy, methyl etc. provided that both A<sup>h</sup> and B<sup>h</sup> are not hydrogen;

R<sup>1h</sup> is phenyl, benzyl, phenethyl or substituted phenyl etc.;

each R<sup>2h</sup> and R<sup>3h</sup> are hydrogen, phenyl, phenylalkyl etc.;

and their acid addition salts, being useful as hypotensives or bronchodilators,

(3) Soviet Union Patent No. 461621 discloses the compounds of the formula:



(J)

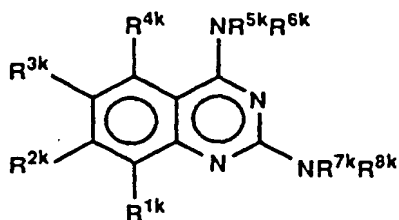
wherein R<sup>j</sup> is hydrogen, lower alkyl or lower alkoxy;

R<sup>1j</sup> is hydrogen or lower alkyl;

R<sup>2j</sup> is phenyl etc.;

R<sup>3j</sup>, R<sup>4j</sup> and R<sup>5j</sup> are hydrogen, halogen, nitro etc.;  
and their salts, being useful as a medicine;

(4) WO-8905297 discloses the compounds of the formula:

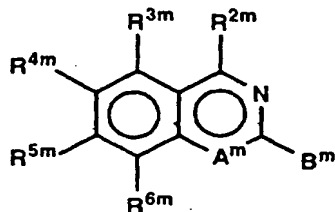


(K)

wherein

each R<sup>1k</sup>, R<sup>2k</sup>, R<sup>3k</sup> and R<sup>4k</sup> are hydrogen, alkyl, alkoxy, amino, alkylamino, dialkylamino, halogen, trifluoromethyl etc.;  
each R<sup>5k</sup> and R<sup>6k</sup> are hydrogen, C1-4 alkyl, -(CH<sub>2</sub>)<sub>n</sub>Ar in which n is 0-4 and Ar is optionally substituted phenyl, etc.;  
R<sup>7k</sup> and R<sup>8k</sup>, taken together with a nitrogen to which these groups bond, are saturated or unsaturated carbocyclic ring, etc.;  
and their salts; having inhibitory effect on H<sup>+</sup>K<sup>+</sup>ATPase and being useful as antiulcer agents.

As to 4-aminoquinazoline derivatives having a cyclic group at the 2nd position thereof or as N-substituent,  
(5) USP-4269834 discloses a complex of a copper salt (III) and the compounds of the formula:

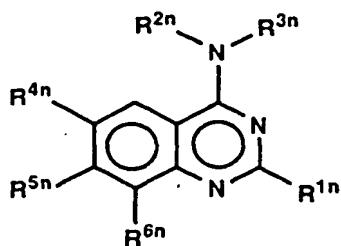


(M)

wherein

A<sup>m</sup> is nitrogen etc.;  
B<sup>m</sup> is 2-optionally substituted-6-pyridyl or 1,5-optionally substituted-2-imidazolyl;  
R<sup>2m</sup> is amino, alkylamino, dialkylamino etc.;  
each R<sup>3m</sup>, R<sup>4m</sup>, R<sup>5m</sup> and R<sup>6m</sup> are hydrogen, halogen, alkyl etc.;  
and their acid addition salts, being useful as agents for the treatment of mycoplasma infections,

(6) USP-3819628 discloses the compounds of the formula:

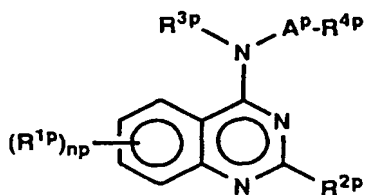


(N)

wherein

R<sup>1n</sup> is optionally substituted phenyl;  
 each R<sup>2n</sup> and R<sup>3n</sup> are hydrogen, C1-4 alkyl, -CH<sub>2</sub>(CH<sub>2</sub>)<sub>nn</sub>ONO<sub>2</sub> etc.;  
 each R<sup>4n</sup>, R<sup>5n</sup> and R<sup>6n</sup> are hydrogen, C1-3 alkyl, C1-3 alkoxy etc.;  
 provided that more than two groups are not alkyl;  
 and their salts; being useful as anti-angina agents,

(7) USP-3971783 discloses the compounds of the formula:

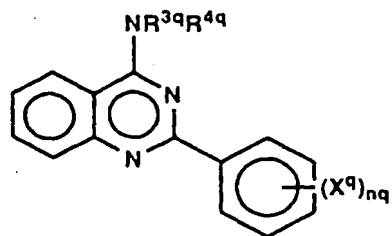


(P)

wherein

R<sup>1p</sup> is halogen, lower alkyl, lower alkoxy etc.;  
 R<sup>2p</sup> is hydrogen, halogen, lower alkyl, lower alkoxy-lower alkyl etc.;  
 R<sup>3p</sup> is hydrogen, lower alkyl etc.;  
 R<sup>4p</sup> is aromatic N-containing heterocyclic;  
 AP is C1-4 alkylene;  
 np is 0-3;  
 and their acid addition salts; being useful as cardiac stimulants,

(8) USP-4306065 discloses the compounds of the formula:

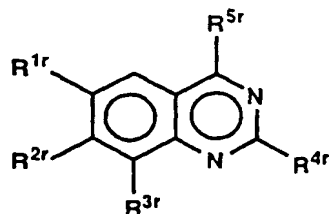


(Q)

wherein

R<sup>3q</sup> is 4-cyanocycloalkyl-alkyl etc.;  
 R<sup>4q</sup> is hydrogen or alkyl;  
 X<sup>q</sup> is hydrogen, alkyl, alkoxy, nitro, amino or halogen;  
 nq is 1-3;  
 and their acid addition salts and hydrates; being useful as hypotensives,

(9) JP Kokai No. 58-172379 discloses the compounds of the formula:

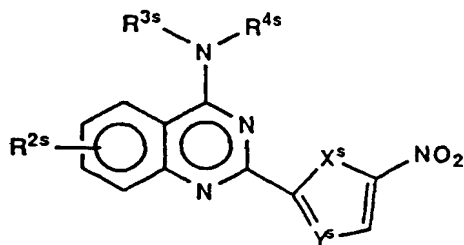


(R)

each

R<sup>1r</sup> and R<sup>3r</sup> are lower alkyl;  
 R<sup>2r</sup> is optionally branched alkoxy carbonyl;  
 R<sup>4r</sup> is hydrogen, alkyl or phenyl;  
 R<sup>5r</sup> is amino, alkylamino, dialkylamino etc; being useful as vasodilators,

(10) Swiss Patent No. 578556 discloses the compounds of the formula:



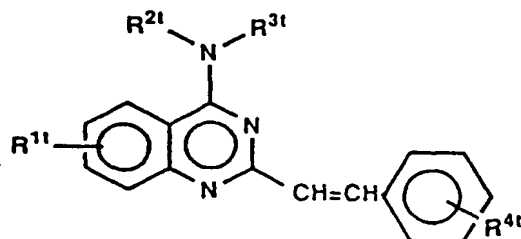
(S)

wherein

R<sup>3s</sup> is hydrogen, lower alkyl etc.;  
 R<sup>4s</sup> is hydrogen, amino, lower hydroxyalkyl, lower alkyl etc.;  
 R<sup>2s</sup> is hydrogen, lower alkyl, lower alkoxy etc.;  
 X<sup>s</sup> is -O-, -S- or -N= and Y<sup>s</sup> is -N=, or X<sup>s</sup> is -N= and Y<sup>s</sup> is -CH=;  
 and their acid addition salts; having bactericidal activity,

(11) USP-3753981 discloses the compounds of the formula:





(T)

wherein

R<sup>11</sup> is hydrogen, lower alkyl, lower alkoxy etc.;  
each R<sup>21</sup> and R<sup>31</sup> are hydrogen, lower alkyl, hydroxy-(lower alkyl) etc.;  
and their acid addition salts; having anti-inflammatory activity.

[0016] EP-A-0135975 discloses a class of compounds including 2-substituted 4-aminoquinazoline derivatives. The compounds are said to have a biocidal activity.

[0017] GB-A-2002746 discloses complexes of a copper salt, having an acceptable anion, with an organic compound of specified general formula. The general formula includes 2-substituted 4-aminoquinazoline derivatives. The complexes are said to be useful for combatting mycoplasma-induced diseases in animals and plants. Some of the compounds covered by the general formula are said to be antihypotensive agents.

[0018] FR-A-2310756 discloses a class of compounds including 2-substituted 4-aminoquinazoline derivatives. The compounds are said to have an antiparasitic activity.

[0019] FR-A-2102221, FR-A-2081456 and FR-A-1460221 disclose 2-substituted 4-aminoquinazoline derivatives which are said to be useful as antimicrobial agents.

[0020] US-A-3956495 discloses 2,4-diaminoquinazoline derivatives which are said to be useful as antithrombotic agents.

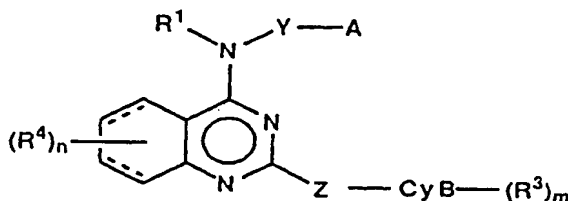
[0021] US-A-3511836 discloses a class of compounds including 2-substituted 4-aminoquinazoline derivatives. The compounds are said to be useful as hypotensive agents.

[0022] WO-A-9307124, which was published between the first and second priority dates of the present application, discloses a broad range of nitrogenous heterocyclic compounds including 2-substituted 4-aminoquinazoline derivatives. The compounds are said to exhibit phosphodiesterase, particularly cGMP-PDE, inhibiting activity.

[0023] Energetic investigation has been carried out in order to discover compounds having inhibitory activities on cGMP-PDE or additionally TXA<sub>2</sub> synthetase, and as a result, the present inventors have found the compound of the present invention.

[0024] There is no description of compounds of the formula (I) in any of the related art disclosing compounds in the formulae (D) and (G) to (T) mentioned above. Accordingly, the compounds of the present invention are quite novel. Furthermore, the fact that compounds of the present invention have inhibitory activity on cGMP-PDE or additionally TXA<sub>2</sub> synthetase, is not suggested from pharmaceutical use disclosed in any of the related art mentioned above. Additionally, the inhibitory activity on cGMP-PDE or TXA<sub>2</sub> synthetase, of the compounds of the present invention, is superior to that of the compounds described in any of the related art mentioned above.

[0025] The present invention accordingly provides a quinazoline derivative of the formula:



(I)

wherein

[1] ----- represents a single or double bond;

R<sup>1</sup> is hydrogen or C1-4 alkyl;

Y is C1-6 alkylene;

A is -O-R<sup>0</sup> or -S(O)<sub>p</sub>-R<sup>0</sup>, in which R<sup>0</sup> is hydroxy-C1-4 alkyl, p is 0-2;

Z is single bond, methylene, ethylene, vinylene or ethynylene;

CyB is

- (1) a 4-7 membered heteroaryl containing one nitrogen atom,
- (2) a 4-7 membered heteroaryl containing two nitrogen atoms,
- (3) a 4-7 membered heteroaryl containing three nitrogen atoms,
- (4) a 4-7 membered heteroaryl containing one or two oxygen atoms,
- (5) a 4-7 membered heteroaryl containing one or two sulfur atoms,

R<sup>3</sup> is hydrogen, C1-4 alkyl, C1-4 alkoxy, halogen or trifluoromethyl;

R<sup>4</sup> is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) -COOR<sup>8</sup>, in which R<sup>8</sup> is hydrogen or C1-4 alkyl, (5) -NR<sup>9</sup>R<sup>10</sup>, in which R<sup>9</sup> is hydrogen, C1-4 alkyl or phenyl(C1-4 alkyl) and R<sup>10</sup> is hydrogen or C1-4 alkyl, (6) -NHCOR<sup>11</sup>, in which R<sup>11</sup> is C1-4 alkyl, (7) -NH<sub>2</sub>SO<sub>2</sub>R<sup>11</sup>, in which R<sup>11</sup> is as hereinbefore defined, (8) SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, in which R<sup>9</sup> and R<sup>10</sup> are as hereinbefore defined, (9) -OCOR<sup>11</sup>, in which R<sup>11</sup> is as hereinbefore defined, (10) halogen, (11) trifluoromethyl, (12) hydroxy, (13) nitro, (14) cyano, (15) -SO<sub>2</sub>N=CHNR<sup>12</sup>R<sup>13</sup> in which R<sup>12</sup> is hydrogen or C1-4 alkyl and R<sup>13</sup> is C1-4 alkyl, (16) -CONR<sup>14</sup>R<sup>15</sup> in which R<sup>14</sup> is hydrogen, C1-4 alkyl or phenyl (C1-4 alkyl) and R<sup>15</sup> is C1-4 alkyl, (17) C1-4 alkylthio, (18) C1-4 alkylsulfinyl, (19) C1-4 alkylsulfonyl, (20) ethynyl, (21) hydroxymethyl, (22) tri(C1-4 alkyl)silylethynyl or (23) acetyl;

m and n independently are 1 or 2;

[2] -----, R<sup>1</sup>, p, Z, CyB, R<sup>3</sup>, m, n are as hereinbefore defined;

Y is bond or C1-6 alkylene;

A is

- (i) -CyA-(R<sup>2</sup>)I, or
- (ii) -O-R<sup>0</sup> or -S(O)<sub>p</sub>-R<sup>0</sup>,

in which R<sup>0</sup> is hydrogen, C1-4 alkyl or -CyA-(R<sup>2</sup>)I,

CyA is

- (1) a 3-7 membered, saturated or unsaturated carbocycle,
- (2) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom,
- (3) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom and one oxygen atom,
- (4) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom and two oxygen atoms,
- (5) a 4-7 membered, unsaturated or partially saturated heterocycle containing two nitrogen atoms and one oxygen atom,
- (6) a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two sulfur atoms,
- (7) a 4-7 membered, unsaturated, partially saturated or fully saturated heterocycle containing one or two oxygen atoms;

R<sup>2</sup> is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) -COOR<sup>5</sup>, in which R<sup>5</sup> is hydrogen or C1-4 alkyl, (5) -NR<sup>6</sup>R<sup>7</sup>, in which R<sup>6</sup> and R<sup>7</sup> independently are hydrogen or C1-4 alkyl, (6) -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, in which R<sup>6</sup> and R<sup>7</sup> are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro or (10) trifluoromethoxy;

I is 1 or 2;

when Z is methylene, ethylene, vinylene or ethynylene,

R<sup>4</sup> is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) -COOR<sup>8</sup>, in which R<sup>8</sup> is hydrogen or C1-4 alkyl, (5) -NR<sup>9</sup>R<sup>10</sup>, in which R<sup>9</sup> is hydrogen, C1-4 alkyl or phenyl(C1-4 alkyl) and R<sup>10</sup> is hydrogen or C1-4 alkyl, (6) -NHCOR<sup>11</sup>, in which

R<sup>11</sup> is C1-4 alkyl, (7) -NH<sub>2</sub>SO<sub>2</sub>R<sup>11</sup>, in which R<sup>11</sup> is as hereinbefore defined, (8) SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, in which R<sup>9</sup> and R<sup>10</sup> are as hereinbefore defined, (9) -OCOR<sup>11</sup>, in which R<sup>11</sup> is as hereinbefore defined, (10) halogen, (11)

trifluoromethyl, (12) hydroxy, (13) nitro, (14) cyano, (15)  $-\text{SO}_2\text{N}=\text{CHNR}^{12}\text{R}^{13}$  in which  $\text{R}^{12}$  is hydrogen or C1-4 alkyl and  $\text{R}^{13}$  is C1-4 alkyl, (16)  $-\text{CONR}^{14}\text{R}^{15}$  in which  $\text{R}^{14}$  is hydrogen, C1-4 alkyl or phenyl(C1-4 alkyl) and  $\text{R}^{15}$  is C1-4 alkyl, (17) C1-4 alkylthio, (18) C1-4 alkylsulfinyl, (19) C1-4 alkylsulfonyl, (20) ethynyl, (21) hydroxymethyl, (22) tri(C1-4 alkyl)silylethynyl or (23) acetyl;

when Z is single bond,

$\text{R}^4$  is (1)  $-\text{NHSO}_2\text{R}^{11}$ , in which  $\text{R}^{11}$  is as hereinbefore defined, (2)  $\text{SO}_2\text{NR}^9\text{R}^{10}$ , in which  $\text{R}^9$  and  $\text{R}^{10}$  are as hereinbefore defined, (3)  $-\text{OCOR}^{11}$ , in which  $\text{R}^{11}$  is as hereinbefore defined, (4) hydroxy, (5)  $-\text{SO}_2\text{N}=\text{CHNR}^{12}\text{R}^{13}$  in which  $\text{R}^{12}$  and  $\text{R}^{13}$  are as hereinbefore defined, (6)  $-\text{CONR}^{14}\text{R}^{15}$  in which  $\text{R}^{14}$  and  $\text{R}^{15}$  are as hereinbefore defined, (7) ethynyl, or (8) tri(C1-4 alkyl)silylethynyl;

[3]  $-----$ ,  $\text{R}^1$ , p, CyB,  $\text{R}^3$ , m, n, CyA and I are as hereinbefore defined;

Y is bond or C1-6 alkylene;

A is

(i)-CyA-( $\text{R}^2$ )I, in which  $\text{R}^2$  is (1)  $-\text{NR}^6\text{R}^7$ , in which  $\text{R}^6$  and  $\text{R}^7$  independently are hydrogen or C1-4 alkyl (with the proviso that  $\text{R}^6$  and  $\text{R}^7$  are not hydrogen at same time), (2)  $-\text{SO}_2\text{NR}^6\text{R}^7$ , in which  $\text{R}^6$  and  $\text{R}^7$  independently are hydrogen or C1-4 alkyl, or (3) trifluoromethoxy; or

(ii)  $-\text{O}-\text{R}^0$ , in which  $\text{R}^0$  is  $-\text{CyA}-(\text{R}^2)\text{I}$ ; or

$-\text{S}(\text{O})\text{p}-\text{R}^0$ , in which  $\text{R}^0$  is hydrogen, C1-4 alkyl or  $-\text{CyA}-(\text{R}^2)\text{I}$ ;

in which  $\text{R}^2$  is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4)  $-\text{COOR}^5$ , in which  $\text{R}^5$  is hydrogen or C1-4 alkyl, (5)  $-\text{NR}^6\text{R}^7$ , in which  $\text{R}^6$  and  $\text{R}^7$  independently are hydrogen or C1-4 alkyl, (6)  $-\text{SO}_2\text{NR}^6\text{R}^7$ , in which  $\text{R}^6$  and  $\text{R}^7$  are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro or (10) trifluoromethoxy;

Z is single bond;

$\text{R}^4$  is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4)  $-\text{COOR}^8$ , in which  $\text{R}^8$  is hydrogen or C1-4 alkyl, (5)  $-\text{NR}^9\text{R}^{10}$ , in which  $\text{R}^9$  is hydrogen, C1-4 alkyl or phenyl(C1-4 alkyl) and  $\text{R}^{10}$  is hydrogen or C1-4 alkyl, (6)  $-\text{NHCOR}^{11}$ , in which  $\text{R}^{11}$  is C1-4 alkyl, (7) halogen, (8) trifluoromethyl, (9) nitro, (10) cyano, (11) C1-4 alkylthio, (12) C1-4 alkylsulfinyl, (13) C1-4 alkylsulfonyl, (14) hydroxymethyl or (15) acetyl;

with the proviso that

(1)  $-\text{CyA}-(\text{R}^2)\text{I}$  does not represent a cyclopentyl and trifluoromethylphenyl, when Y is a single bond;

(2) CyB does not bond to Z through a nitrogen atom, when Z is vinylene or ethynylene;

(3) CyB is not pyridine orthiophene when CyA is a 4-7 membered unsaturated, partially saturated or fully saturated heterocycle containing one or two oxygen atoms;

(4) Y is not a single bond, when A is (ii)  $-\text{O}-\text{R}^0$  or  $-\text{S}(\text{O})\text{p}-\text{R}^0$ ; or a compound which is:

- (1) 4-phenylmethylamino-2-(3-pyridyl)quinazoline,
- (2) 4-(3-methylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (3) 4-(3,4-dimethoxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (4) 4-(4-carboxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (5) 4-(3-chlorophenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (6) 4-(3-trifluoromethylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (7) 4-(3-nitrophenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (8) 4-phenylmethylamino-2-(6-chloro-3-pyridyl)quinazoline,
- (9) 4-phenylmethylamino-6-methyl-2-(3-pyridyl)quinazoline,
- (10) 4-phenylmethylamino-6,7-dimethoxy-2-(3-pyridyl)quinazoline,
- (11) 4-phenylmethylamino-6-acetylamino-2-(3-pyridyl)quinazoline,
- (12) 4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline,
- (13) 4-phenylmethylamino-6-bromo-2-(3-pyridyl)quinazoline,
- (14) 4-phenylmethylamino-7-fluoro-2-(3-pyridyl)quinazoline,
- (15) 4-phenylmethylamino-6-nitro-2-(3-pyridyl)quinazoline,
- (16) 4-phenylamino-2-(3-pyridyl)quinazoline,
- (17) 4-(3-methoxycarbonylphenyl)amino-2-(3-pyridyl)quinazoline,
- (18) 4-phenylethylamino-2-(3-pyridyl)quinazoline,
- (19) 4-phenylmethylamino-2-(2-pyridyl)quinazoline,
- (20) 4-phenylmethylamino-2-(4-pyridyl)quinazoline,
- (21) 6-iodo-4-phenylmethylamino-2-(3-pyridyl)quinazoline,

- (22) 4-(3-carboxyphenyl)amino-2-(4-pyridyl)quinazoline,  
 (23) 6-fluoro-4-phenylmethylamino-2-(3-pyridyl)quinazoline,  
 (24) 4-(cyclopropylmethyl)amino-2-(3-pyridyl)quinazoline,  
 (25) 4-(3-pyridylmethyl)amino-2-(3-pyridyl)quinazoline,  
 (26) 4-(2-thienylmethyl)amino-2-(3-pyridyl)quinazoline,  
 (27) 4-(2-furylmethyl)amino-2-(1-imidazolyl)quinazoline,  
 (28) 4-(2-tetrahydrofuranylmethyl)amino-2-(1-imidazolyl)quinazoline,  
 (29) 4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,  
 (30) 6-methoxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,  
 (31) 6-chloro-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,  
 (32) 4-(2-thienylmethyl)amino-2-(1-imidazolyl)quinazoline,  
 (33) 6-acetyl-4-(2-methoxyethyl)amino-2-(3-pyridyl)quinazoline,  
 (34) 4-phenylmethylamino-6-methoxy-2-(1-imidazolyl)quinazoline,  
 (35) 4-phenylmethylamino-6,7-dimethoxy-2-(1-imidazolyl)quinazoline,  
 (36) 4-phenylmethylamino-6-carboxy-2-(1-imidazolyl)quinazoline,  
 (37) 4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline,  
 (38) 4-phenylmethylamino-6-bromo-2-(1-imidazolyl)quinazoline,  
 (39) 4-phenylmethylamino-6-nitro-2-(1-imidazolyl)quinazoline,  
 (40) 4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 (41) 4-phenylmethylamino-2-(2-methyl-1-imidazolyl)quinazoline,  
 (42) 7-chloro-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 (43) 4-(3,4-dimethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline,  
 (44) 4-(2-phenylethyl)amino-2-(1-imidazolyl)quinazoline,  
 (45) 4-cyclohexylmethylamino-2-(1-imidazolyl)quinazoline,  
 (46) 6-iodo-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 (47) 4-phenylmethylamino-2-(1-triazolyl)quinazoline,  
 (48) 4-phenylmethylamino-6,8-diiodo-2-(1-imidazolyl)quinazoline,  
 (49) 4-phenylmethylamino-2-(2-thienyl)quinazoline,  
 (50) 4-phenylmethylamino-2-(2-furyl)quinazoline,  
 (51) 4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,  
 (52) 6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline, or  
 (53) 6-ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline;

or a pharmaceutically acceptable salt thereof or a hydrate thereof.

[0026] The present invention also provides a process for the preparation of a compound of the formula (I).

[0027] The present invention also provides a pharmaceutical composition for the treatment of mammals, including humans, comprising as active ingredient, an effective amount of a compound of the formula (I), a pharmaceutically acceptable salt thereof or a hydrate thereof in association with a pharmaceutically acceptable carrier or coating.

[0028] The present invention also provides a compound of the formula (I), a pharmaceutically acceptable salt thereof or a hydrate thereof, for use as a medicament in the treatment of mammals.

[0029] In the formula (I), the C1-4 alkyl group represented by R<sup>0</sup>, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup> and R<sup>15</sup> mean methyl, ethyl, propyl, butyl and the isomers thereof.

[0030] In the formula (I), the C1-4 alkoxy group represented by R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> mean methoxy, ethoxy, propoxy, butoxy and isomers thereof.

[0031] In the formula (I), the halogen atom represented by R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> mean fluorine, chlorine, bromine and iodine.

[0032] In the formula (I), the C1-6 alkylene group represented by Y means methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene and isomers thereof.

[0033] In the formula (I), examples of 3-7 membered, saturated or unsaturated, monocyclic carbocyclic ring, represented by Cya-(1), are cyclobutadiene, cyclopentadiene, benzene, cycloheptatriene ring, and partially or fully saturated rings thereof, for example, cyclobutane, cyclopentane, cyclohexane, cycloheptane ring, and cyclopropane ring.

[0034] In the formula (I), heterocyclic mono-ring of 4-7 membered containing one nitrogen atom, unsaturated or partially saturated represented by CyA-(2) is, for example, azepine, pyridine, pyrrole, isomeric rings thereof and partially saturated rings thereof.

[0035] In the formula (I), heterocyclic mono-ring of 4-7 membered containing one nitrogen atom and one oxygen atom, unsaturated or partially saturated represented by CyA-(3) is, for example, oxyazepine, oxazine, oxyazole, isomeric rings thereof and partially saturated rings thereof.

[0036] In the formula (I), heterocyclic mono-ring of 4-7 membered containing one nitrogen atom and two oxygen

atom, unsaturated or partially saturated represented by CyA-(4) is, for example, dioxazepine, dioxazine, dioxazole, isomeric rings thereof and partially saturated rings thereof.

[0037] In the formula (I), heterocyclic mono-ring of 4-7 membered containing two nitrogen atom and one oxygen atom, unsaturated or partially saturated represented by CyA-(5) is, for example, oxadiazepine, oxadiazine, oxadiazole, isomeric rings thereof and partially saturated rings thereof.

[0038] In the formula (I), heterocyclic mono-ring of 4-7 membered containing one or two sulfur atom, unsaturated or partially saturated represented by CyA-(6) is, for example, thiepin, thiophene, thian, dithian, isomeric rings thereof and partially saturated rings thereof.

[0039] In the formula (I), heterocyclic mono-ring of 4-7 membered containing two oxygen atoms, unsaturated or fully or partially saturated represented by CyA-(7) is, for example, oxepin, pyran, dioxin, furan, isomeric rings thereof and fully or partially saturated rings thereof.

[0040] In the formula (I), 4-7 membered heteroaryl containing one nitrogen atom represented by CyB-(1) is, for example, azepine, pyridine, pyrrole and isomeric rings thereof.

[0041] In the formula (I), 4-7 membered heteroaryl containing two nitrogen atoms represented by CyB-(2) is, for example, diazepine, diazine, diazole and isomeric rings thereof.

[0042] In the formula (I), 4-7 membered heteroaryl containing three nitrogen atoms represented by CyB-(3) is, for example, triazepine, triazine, triazole and isomeric rings thereof.

[0043] In the formula (I), 4-7 membered heteroaryl containing one or two oxygen atoms represented by CyB-(4) is, for example, oxepin, pyran, dioxin, furan, isomeric rings thereof or partially saturated rings thereof.

[0044] In the formula (I), 4-7 membered heteroaryl containing one or two oxygen atoms represented by CyB-(5) is, for example, thiepin, thiophene, thian, dithian and isomeric rings thereof.

[0045] Examples of representative compounds of the present invention are listed as follows:

4-phenylmethylamino-2-(3-pyridyl)quinazoline,  
 4-(3-methylphenylmethyl)amino-2-(3-pyridyl)quinazoline,  
 4-(3,4-dimethoxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,  
 4-(4-carboxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,  
 4-(4-(N,N-dimethylamino)phenylmethyl)amino-2-(3-pyridyl)quinazoline,  
 4-(4-sulfamoylphenylmethyl)amino-2-(3-pyridyl)quinazoline,  
 4-(3-chlorophenylmethyl)amino-2-(3-pyridyl)quinazoline,  
 4-(3-trifluoromethylphenylmethyl)amino-2-(3-pyridyl)quinazoline,  
 4-(3-nitrophenylmethyl)amino-2-(3-pyridyl)quinazoline,  
 4-phenylmethylamino-2-(6-chloro-3-pyridyl)quinazoline,  
 4-phenylmethylamino-6-methyl-2-(3-pyridyl)quinazoline,  
 4-phenylmethylamino-6,7-dimethoxy-2-(3-pyridyl)quinazoline,  
 4-phenylmethylamino-6-acetylamino-2-(3-pyridyl)quinazoline,  
 4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline,  
 4-phenylmethylamino-6-bromo-2-(3-pyridyl)quinazoline,  
 4-phenylmethylamino-7-fluoro-2-(3-pyridyl)quinazoline,  
 4-phenylmethylamino-6-nitro-2-(3-pyridyl)quinazoline,  
 4-phenylmethylamino-6-methoxy-2-(1-imidazolyl)quinazoline,  
 4-phenylmethylamino-6,7-dimethoxy-2-(1-imidazolyl)quinazoline,  
 4-phenylmethylamino-6-carboxy-2-(1-imidazolyl)quinazoline,  
 4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline,  
 4-phenylmethylamino-6-bromo-2-(1-imidazolyl)quinazoline,  
 4-phenylmethylamino-6-hydroxy-2-(1-imidazolyl)quinazoline,  
 4-phenylmethylamino-6-nitro-2-(1-imidazolyl)quinazoline,  
 4-phenylamino-2-(3-pyridyl)quinazoline,  
 4-(3-methoxycarbonylphenyl)amino-2-(3-pyridyl)quinazoline,  
 4-phenethylamino-2-(3-pyridyl)quinazoline,  
 4-(cyclopropylmethyl)amino-2-(3-pyridyl)quinazoline,  
 4-(3-pyridylmethyl)amino-2-(3-pyridyl)quinazoline,  
 4-(2-thienylmethyl)amino-2-(3-pyridyl)quinazoline,  
 4-phenylmethylamino-2-(2-pyridyl)quinazoline,  
 4-phenylmethylamino-2-(4-pyridyl)quinazoline,  
 4-phenylmethylamino-2-(2-(3-pyridyl)vinyl)quinazoline,  
 4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 4-phenylmethylamino-2-((1-imidazolyl)methyl)quinazoline,

4-phenylmethylamino-2-(2-methyl-1-imidazolyl)quinazoline,  
 4-phenylmethylamino-2-(1-triazolyl)quinazoline,  
 4-phenylmethylamino-2-(2-thienyl)quinazoline,  
 4-phenylmethylamino-2-(2-furyl)quinazoline,  
 5 6-acetyloxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline,  
 6-chloro-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline,  
 6-hydroxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline,  
 6-acetyloxy-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,  
 6-hydroxy-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,  
 10 6-methyl-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,  
 6-methoxy-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,  
 6,7-dimethoxy-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,  
 6-acetyloxy-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,  
 6-chloro-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,  
 15 6-bromo-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,  
 6-iodo-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,  
 7-fluoro-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,  
 6-hydroxy-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,  
 6-nitro-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,  
 20 6-methyl-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,  
 6-methoxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-quinazoline,  
 6,7-dimethoxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-quinazoline,  
 6-acetyloxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-quinazoline,  
 6-bromo-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,  
 25 6-iodo-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,  
 7-fluoro-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,  
 6-hydroxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-quinazoline,  
 6-nitro-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,

and further those described in Examples below are also representative compounds of the present invention.

#### Salts and Acid addition salts

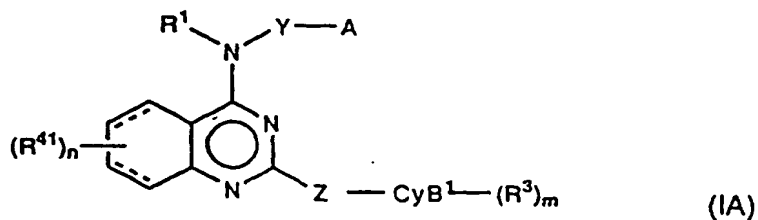
[0046] The compounds of the formula (I), if desired, may be converted into acid addition salts by known methods. Preferably, acid addition salts are non-toxic and water-soluble. The suitable acid addition salts are, for example, salts of an inorganic acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, nitric acid, or an organic acid such as acetic acid, lactic acid, tartaric acid, benzoic acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, isethionic acid, glucuronic acid and gluconic acid.

[0047] The compounds of the formula (I), if desired, may be converted into salts by known methods. Preferable, salts are non-toxic salts and water-soluble. The suitable salts are salts of alkaline metal (sodium, potassium etc.), salts of alkaline earth metal (calcium, magnesium etc.), ammonium salts, salts of pharmaceutically acceptable organic amine (tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, phenylmethylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)methylamine, lysine, arginine, N-methyl-D-glucamine etc.).

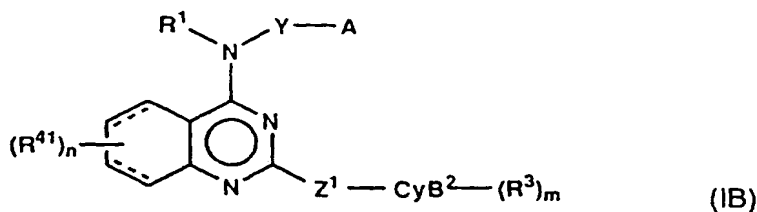
[0048] Throughout the specification including claims, it may be easily understood by those skilled in the art, that the alkyl, alkoxy, groups include straight- chained and also branched-chained ones. Accordingly, all isomers produced by the difference in stereo configuration, such as asymmetric carbons are included in the present invention.

#### Preparations

[0049] According to the present invention, of the compounds of the present invention, the compounds of the formula:



15 wherein  $R^{41}$  is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4)  $-COOR^8$ , (5)  $-NR^9R^{10}$ , in which  $R^9$  and  $R^{10}$  are as hereinbefore defined, provided that both  $R^9$  and  $R^{10}$  are not hydrogen, (6)  $SO_2NR^9R^{10}$ , in which  $R^9$  and  $R^{10}$  are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro, (10) cyano, (11) C1-4 alkylthio, (12) tri(C<sub>1-4</sub> alkyl)silylethynyl, (13)  $-SO_2N=CHNR^{12}R^{13}$ , in which  $R^{12}$  and  $R^{13}$  are as hereinbefore defined, or (14)  $-CONR^{14}R^{15}$ , in which  $R^{14}$  and  $R^{15}$  are as hereinbefore defined,  $CyB^1$  is as hereinbefore defined for  $CyB$ , provided that a carbon atom in the ring should bond to Z, and the other symbols are as hereinbefore defined; and the compounds of the formula:

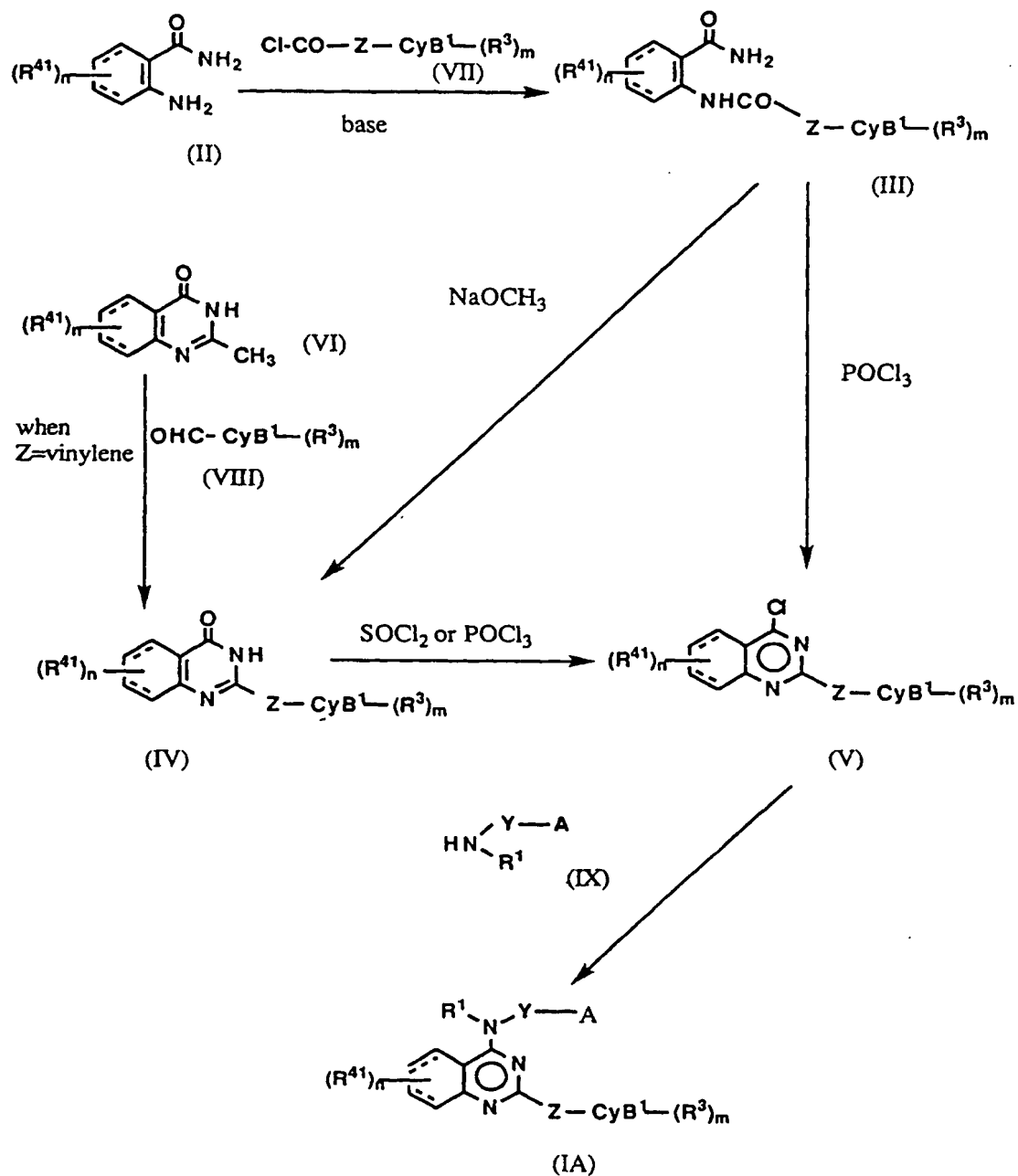


30 wherein  $Z^1$  is single bond or methylene,  $CyB^2$  is as hereinbefore defined for  $CyB$ , provided that a nitrogen atom in the ring should bond to  $Z^1$ ,

and the other symbols are as hereinbefore defined;

35 may be prepared by using a series of reactions depicted in Scheme A and B, respectively, wherein  $R^{50}$  is C<sub>1-4</sub> alkyl and the other symbols are as hereinbefore defined.

Scheme A





Chemical reaction scheme for the synthesis of compound (IB):

Starting materials (XVIII), (II), and (XVII) are converted to intermediate (X):

- (XVIII) reacts with  $\text{H}_2\text{N}-\text{C}(=\text{O})-\text{NH}_2$  to form (X).
- (II) reacts with phosgene to form (X).
- (XVII) reacts with 1)  $\text{KOCN}/\text{AcOH}$ , 2)  $\text{NaOH}$ , and 3)  $\text{HCl}$  to form (X).

Intermediate (X) is converted to (XI) using  $\text{POCl}_3$ .

(XI) reacts with compound (IX) ( $\text{HN}(\text{R}^1)-\text{Y}-\text{A}$ ) to form (XII).

(XII) reacts with compound (XV) ( $\text{NC}-\text{CH}_2-\text{Cl}$ ) to form (XIV).

(XIV) reacts with compound (IX) ( $\text{HN}(\text{R}^1)-\text{Y}-\text{A}$ ) to form (XII).

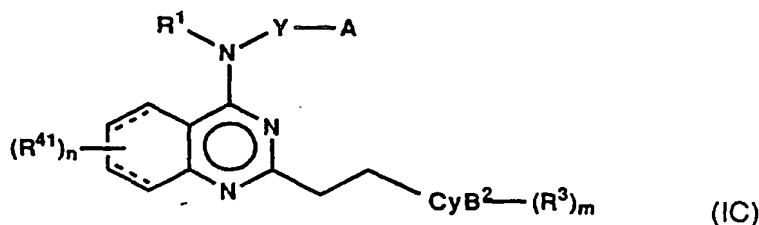
(XII) reacts with compound (XVI) ( $\text{H}-\text{CyB}^2-(\text{R}^3)_m$ ) to form the final product (IB).

**[0051]** For example, the compounds of the formula (IA) may be prepared from those of the formula (V) by the reaction with an amine of the formula (IX) in a proper organic solvent such as a lower alkanol (e.g. ethanol) or tetrahydrofuran,

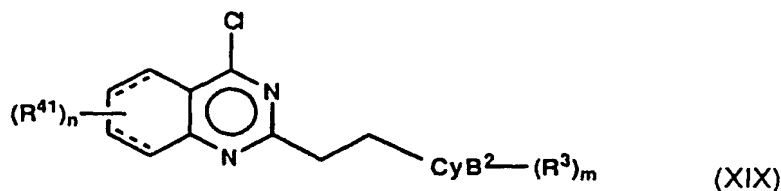
or a mixture thereof, at a temperature from ambient to reflux, for several hours to several days, if necessary in the presence of a base such as triethylamine.

[0052] Further, the compounds of the formula (IB) may be prepared from those of the formula (XII) by the reaction with a cyclic amine of the formula (XVI) in phenol at a reflux temperature for several hours.

[0053] Furthermore, the compounds of the present invention, of the formula:



wherein the various symbols are as hereinbefore defined; may be prepared from those of the formula:



wherein the various symbols are as hereinbefore defined; by the methods described hereinbefore for the conversion of the compounds of the formula (V) into those of the formula (IA). The compounds of the formula (XIX) may be prepared by the methods similar to those described hereinbefore in Scheme A.

[0054] On the other hand, the compounds of the formula (I) other than those of the formulae (IA), (IB) and (IC) may be prepared by the methods known per se described below.

[0055] The compounds of the formula (I) wherein R<sup>4</sup> is amino may be prepared from those wherein R<sup>4</sup> is nitro, by the reduction with zinc etc. in a proper organic solvent.

[0056] The compounds of the formula (I) wherein R<sup>4</sup> is hydroxy may be prepared from those wherein R<sup>4</sup> is alkoxy such as methoxy, by the reaction with hydrogen bromide or tribromoboron.

[0057] The compounds of the formula (I) wherein R<sup>4</sup> is -NHCOR<sup>11</sup>, wherein R<sup>11</sup> is as hereinbefore defined, may be prepared from those wherein R<sup>4</sup> is nitro, by the reaction with the corresponding organic acid such as acetic acid in the presence of zinc dust.

[0058] The compounds of the formula (I) wherein R<sup>4</sup> is NHSO<sub>2</sub>R<sup>11</sup>, wherein R<sup>11</sup> is as hereinbefore defined, may be prepared from those wherein R<sup>4</sup> is amino by the reaction with the corresponding alkylsulfonyl chloride such as methanesulfonyl chloride.

[0059] The compounds of the formula (I) wherein R<sup>4</sup> is -OCOR<sup>11</sup>, wherein R<sup>11</sup> is as hereinbefore defined, may be prepared from those wherein R<sup>4</sup> is hydroxy by the esterification with the corresponding organic acid such as acetic acid.

[0060] The compounds of the formula (I) wherein R<sup>4</sup> is C1-4 alkylsulfinyl or C1-4 alkylsulfonyl may be prepared from those wherein R<sup>4</sup> is C1-4 alkylthio by the oxidation by oxidating agent such as hydrogen peroxide.

[0061] The compounds of the formula (I) wherein R<sup>4</sup> is hydroxymethyl may be prepared from those wherein R<sup>4</sup> is alkoxy carbonyl, by the reduction with reducing agent such as lithium borohydride, lithium aluminum hydride etc.

[0062] The compounds of the formula (I) wherein R<sup>4</sup> is ethynyl may be prepared from those wherein R<sup>4</sup> is tri(C1-4 alkyl)silylethynyl, by the removal reaction of silyl group with tetrabutylammonium halide.

[0063] The compounds of the formula (I) wherein R<sup>4</sup> is acetyl may be prepared from those wherein R<sup>4</sup> is ethynyl, by the reaction with mercury sulfate and acetic acid in an acidic condition.

[0064] In each reaction in the present specification, products may be purified by conventional manner. For example, it may be carried out by distillation at atmospheric or reduced pressure, high performance liquid chromatography, thin layer chromatography or column chromatography using silica gel or magnesium silicate, washing or recrystallization.

Purification may be carried out after each reaction, or after a series of reactions.

[0065] The starting materials of the formulae (II), (VI) and (XIII), and each reagents of the formulae (VII), (VIII), (IX), (XV), (XVI), (XVII) and (XVIII) used in the process for the preparation of the present invention are known per se or may be easily prepared by known methods.

#### Effect

[0066] The compounds of the formula (I), pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof, of the present invention have an inhibitory effect on cGMP-PDE, or additionally on TXA<sub>2</sub> synthetase, and are, therefore, useful for the prevention and/or treatment of not only diseases induced by enhancement of the metabolism of cGMP, such as hypertension, heart failure, myocardial infarction, angina, atherosclerosis, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, asthma, bronchitis, dementia, immunodeficiency, but also diseases induced by enhancement of the synthesis of TXA<sub>2</sub> such as inflammation, thrombosis, cerebral apoplexy, asthma, cardiostenosis, cerebral infarction etc, in mammals, especially in humans.

[0067] Especially, it is very useful for the prevention and/or treatment of heart failure, angina pectoris, pulmonary hypertension, various kinds of renal diseases, hyoiuresis induced by heart failure.

[0068] The inhibitory effect on cGMP-PDE and TXA<sub>2</sub> synthetase, of the compounds of the present invention were confirmed by screening tests as described below.

#### (1) Inhibitory effect on cGMP-PDE

##### Method

[0069] PDE IC was isolated from human platelets according to standard methods previously described in Lugnier, C. et al., *Biochem. Pharmacol.* 35: 1743, 1986 (incorporated in its entirety by reference). Typically, connective tissue and adventitia were removed and 1-2 units of platelets were suspended in 10 volumes of buffer A (20 mM Tris-HCl, pH 7.5, containing 2 mM magnesium acetate, 1 mM dithiothreitol, and 5 mM Na<sub>2</sub>EDTA) using a Brinkman polytron. The proteinase inhibitors leupeptin, pepstatin A, and phenylmethyl-sulfonyl fluoride (PMSF) were also included in this buffer (final concentration of 100 nM each). The homogenate was centrifuged at 100,000g for 60 minutes. The supernatant was then removed and filtered through four layers of cheesecloth. The supernatant was applied to a DWAE-Trisacryl M column. The column was washed with several bed volumes of buffer B (20 mM Tris-HCl, pH 7.5, containing 2 mM magnesium acetate, 1 mM dithiothreitol, and proteinase inhibitors) and eluted by two successive linear NaCl gradients (0.05-0.15 M, 300 ml total; 0.15-0.40 M, 200 ml total). Five milliliter fractions were collected and assayed for cyclic GMP PDE activity.

[0070] Phosphodiesterase activity was measured, as described by Thompson, et al., *Adv. Cyclic Nucleotide Res.* 10: 69, 1979 (incorporated in its entirety by reference), in a reaction medium containing 40 mM Tris-HCl (pH 8.0), 5 mM MgCl<sub>2</sub>, and 1 mM dithiothreitol. The concentration of substrate (<sup>3</sup>H-cGMP) was 0.2mM. Compounds of the present invention were dissolved in dimethyl sulfoxide (DMSO) at a final concentration of 2.5%. This concentration of DMSO inhibited enzyme activity by approximately 10%. The IC<sub>50</sub> values (concentration that produced 50% inhibition of substrate hydrolysis) for the compounds examined were determined from concentration-response curves in which concentrations typically ranged from 10<sup>-8</sup> to 10<sup>-3</sup> M for the less potent inhibitors (half-log increments).

##### Result

[0071] The result is shown in Table 1 below.

Table 1

Inhibitory activity on cGMP-PDE		
Compounds	Example No.	Inhibitory activity IC <sub>50</sub> , (M)
3 (e)	(free base)	4.5 x 10 <sup>-7</sup>
3 (i)	(2HCl)	3.6 x 10 <sup>-7</sup>
3 (k)	(3HCl)	2.8 x 10 <sup>-6</sup>
7	(free base)	2.0x 10 <sup>-7</sup>
5	(free base)	2.6x 10 <sup>-7</sup>
3 (t)	(free base)	7.2x 10 <sup>-7</sup>
3(l)	(2HCl)	7.6x 10 <sup>-7</sup>

Table 1 (continued)

Inhibitory activity on cGMP-PDE		
Compounds	Example No.	Inhibitory activity IC <sub>50</sub> , (M)
6 (b)	(2HCl)	3.0x 10 <sup>-6</sup>
6 (a)	(2HCl)	2.8x 10 <sup>-9</sup>
3 (a)	(2HCl)	1.05x 10 <sup>-7</sup>
3 (z)	(2HCl)	1.0x 10 <sup>-8</sup>
3(ff)	(2HCl)	4.2x10 <sup>-9</sup>
6(c)	(2HCl)	2.3x10 <sup>-9</sup>
6(k)	(2HCl)	6.3x10 <sup>-7</sup>
6(l)	(free base)	2.15x10 <sup>-7</sup>
6(o)	(2HCl)	1.3x10 <sup>-7</sup>
8	(2HCl)	8.9x10 <sup>-7</sup>
6(x)	(2HCl)	2.7x10 <sup>-7</sup>
11(e)	(2HCl)	5.5x10 <sup>-7</sup>

(2) Inhibitory effect on TXA<sub>2</sub> synthetase

## Method

[0072] Male Wistar rats were starved overnight. Five hundreds microliter of heparinized (10U/mL) whole blood was collected from abdominal aorta using polyethylene syringe (needle: 22 or 26G). The blood freshly drawn from animal was preincubated with 5  $\mu$ L of test compound at 37 °C. Five minutes later, 2.5  $\mu$ L of 6 mM of Ca ionophore A23187 (final concentration of 30  $\mu$ M) was added into tube, and incubation mixture was further incubated for 15 min. The reaction was terminated by centrifugation of tubes at 12,000 rpm for 2 min. TXB<sub>2</sub> content in the supernatant was determined by EIA as follows.

[0073] One milliliter of 0.5 M glycine-HCl buffer (pH 3.2) was added to 100  $\mu$ L of sample. The samples were mixed well and centrifuged at 1,700 G for 10 min at 4 °C. The extracted supernatant was applied to a SEP-PAK (registered Trade Mark) C<sub>18</sub> cartridge (Waters Assoc.). After washing with 10 mL of distilled water followed by 10 mL each of 15% ethanol and petroleum ether, the sample was eluted with 3 mL of ethyl acetate. The ethyl acetate fraction was evaporated to dryness under gentle N<sub>2</sub> stream and the residue was dissolved in EIA buffer (final volume of 1 mL) following the addition of 300  $\mu$ L of 0.01 M NaHCO<sub>3</sub>-NaOH buffer (pH 10.0). EIA for TXB<sub>2</sub> was carried out according to a legend attached to the kit (Chyman Chemical Co., Inc.). Overall recovery of TXB<sub>2</sub> in this extraction procedure was 90%. The IC<sub>50</sub> values (concentration that produced 50% inhibition of TXB<sub>2</sub> synthesis) for the compounds examined were determined from concentration-response curves.

Table 2

Inhibitory activity on TXA <sub>2</sub> synthetase		
Compounds	Example No.	Inhibitory activity IC <sub>50</sub> , (M)
3 (e)	(free base)	5.8 x 10 <sup>-6</sup>
5	(free base)	2.2 x 10 <sup>-7</sup>
11(e)	(2HCl salt)	1.77x10 <sup>-6</sup>
6(bb)	(2HCl salt)	2.0x10 <sup>-7</sup>
6(kk)	(2HCl salt)	3.6x10 <sup>-6</sup>
6(nn)	(2HCl salt)	1.35x10 <sup>-6</sup>
18(a)	(2HCl salt)	1.33x10 <sup>-6</sup>

[0074] On the other hand, it was confirmed that the acute toxicity of the compound of the present invention is very weak. Therefore, the compounds of the present invention may be considered to be sufficiently safe and suitable for pharmaceutical use.

## Application for Pharmaceuticals

[0075] For the purpose above described, the compounds, of the formula (I), of the present invention, pharmaceutically acceptable salts and acid addition salts thereof and hydrates thereof may be normally administered systemically or partially, usually by oral or parenteral administration.

[0076] The doses to be administered are determined depending upon age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment etc. In the human adult, the doses per person are generally between 1 mg and 1000 mg, by oral administration, up to several times per day, and between 1 mg and 100 mg, by parenteral administration up to several times per day, or continuous administration between 1 and 24 hrs. per day intravenously.

[0077] As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

[0078] Administration of the compounds of the present invention, may be as solid compositions, liquid compositions or other compositions for oral administration, as injections, liniments or suppositories etc. for parenteral administration.

[0079] Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules. Capsules include hard capsules and soft capsules.

[0080] In such compositions, one or more of the active compound(s) is or are, admixed with at least one inert diluent (such as lactose, mannitol, glucose, hydroxypropyl cellulose, micro crystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate etc.) The compositions may also comprise, as is normal practice, additional substances other than inert diluents: e.g. lubricating agents (such as magnesium stearate etc.), disintegrating agents (such as cellulose calcium glycolate etc.), stabilizing agents (such as lactose etc.), and assisting agents for dissolving (such as glutamic acid, aspartic acid etc.).

[0081] The tablets or pills may, if desired, be coated with film of gastric or enteric material (such as sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phthalate etc.), or be coated with more than two films. And further, coating may include containment within capsules of absorbable materials such as gelatin.

[0082] Liquid compositions for oral administration include pharmaceutically-acceptable solutions, emulsions, suspensions, syrups and elixirs.

[0083] In such compositions, one or more of the active compound(s) is or are comprise in inert diluent(s) commonly used in the art (purified water, ethanol etc.).

[0084] Besides inert diluents, such compositions may also comprise adjuvants (such as wetting agents, suspending agents etc.), sweetening agents, flavouring agents, perfuming agents and preserving agents.

[0085] Other compositions for oral administration include spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s).

[0086] Spray compositions may comprise additional substances other than inert diluents: e.g. stabilizing agents (sodium sulfite etc.), isotonic buffer (sodium chloride, sodium citrate, citric acid etc.)

[0087] For preparation of such spray compositions, for example, the method described in the United States Patent No. 2,868,691 or 3,095,355 (herein incorporated in their entireties by reference) may be used.

[0088] Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. In such compositions, one more of active compound(s) is or are admixed with at least one of inert aqueous diluent(s) (distilled water for injection, physiological salt solution etc.) or inert non-aqueous diluent(s) (propylene glycol, polyethylene glycol, olive oil, ethanol, POLYSOLBATE80 (registered trade mark) etc.).

[0089] Injections may comprise additional other than inert diluents: e.g. preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agent (lactose etc.), assisting agents such as assisting agents for dissolving (glutamic acid, aspartic acid etc.).

[0090] They may be sterilized for example, by filtration through a bacteria-retaining filter, by incorporation of sterilizing agents in the compositions or by irradiation. They also be manufactured in the form of sterile solid compositions, for example, by freeze-drying, and which can be dissolved in sterile water or some other sterile diluents for injection immediately before used.

[0091] Other compositions for parenteral administration include liquids for external use, and endermic liniments (ointment etc.), suppositories and pessaries which comprise one or more of the active compound(s) and may be prepared by known methods.

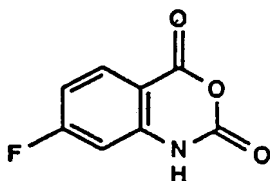
## Reference example and Examples

[0092] The following Reference examples and examples are intended to illustrate the present invention. In Reference examples and examples, "mp" shows "melting point".

Reference example 1

4-fluoroisatoic anhydride

[0093]



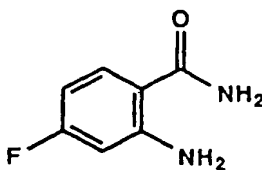
[0094] To a solution of 2-amino-4-fluorobenzoic acid (4.65 g) in 50 mL of mixed solvent (10 : 1 = toluene : tetrahydrofuran) was added phosgene (4.46 g, 1.93 M solution of toluene ) dropwise via a drop funnel. The mixture was stirred at room temperature for 1 hour and then heated to reflux over night. The mixture was concentrated to about 10 mL and cooled in refrigerator. The precipitate was filtered, washed with ether (5 mL X 2) and air-dried to give the title compound (5.43 g) as a white solid having the following physical data.

NMR (200MHz, DMSO-d<sub>6</sub>):  $\delta$  6.92 (dd, 1 H), 7.11 (td, 1 H), 8.00 (dd, 1 H), 11.92 (broad, 1H).

Reference example 2

4-fluoroanthranilamide

[0095]



[0096] A solution of the isatoic anhydride compound (3.62 g, prepared in Reference example 1) in 100 mL of tetrahydrofuran was placed in a 200 mL round bottle equipped with gas in- and outlet. The anhydrous ammonia gas was gently bubbled into the solution for 1.5 to 2 hours. After removal of the solvent the residue was taken up in methylene chloride (30 mL) and water (30 mL). The precipitate was collected by filtration and washed with methylene chloride (10 mL) to give the title compound (1.95 g) as a pale white solid having the following physical data.

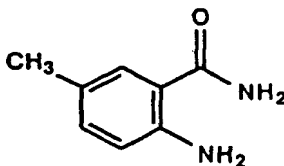
NMR (200MHz, DMSO-d<sub>6</sub>):  $\delta$  6.70 (m, 1H), 6.82 (m, 1H), 6.90 (broad, 2H), 7.72 (m, 1H).

[0097] The following compounds were obtained by the same procedure as Reference example 1 and Reference example 2, by using the corresponding substituted anthranilic acid compound.

Reference example 2(a)

5-methylanthranilamide

[0098]



EP 0 579 496 B1

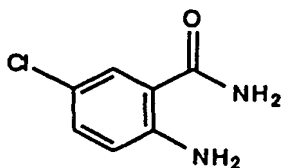
The product was collected by filtration as a pale solid.

NMR (200MHz, DMSO-d6):  $\delta$  2.24 (s, 3H), 5.50 (broad, 2H), 6.62 (d, 1H), 7.07 (dd, 1H), 7.16 (d, 1H).

Reference example 2(b)

5-chloroanthranilamide

[0099]



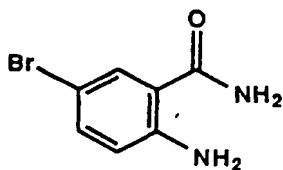
The product was collected by filtration as a pale solid.

NMR (200MHz, DMSO-d6):  $\delta$  5.68 (broad, 2H), 6.64 (d, 1H), 7.20 (dd, 1H), 7.35 (d, 1H).

Reference example 2(c)

5-bromoanthranilamide

[0100]



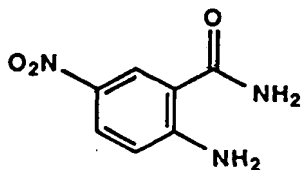
The product was collected by filtration as a pale brown.

NMR (200MHz, DMSO-d6):  $\delta$  6.66 (dd, 1H), 6.72 (broad, 2H), 7.20 (broad, 1H), 7.26 (dt, 1H), 7.70 (t, 1H), 7.82 (broad, 1H).

Reference example 2(d)

5-nitroanthranilamide

[0101]



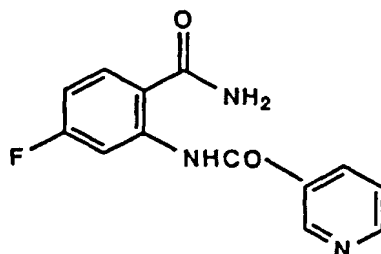
The product was collected by filtration as a solid.

NMR (200MHz, DMSO-d6):  $\delta$  6.80 (dd, 1H), 7.40 (broad, 1H), 7.90 (broad, 2H), 8.03 (dt, 1H), 8.20 (broad, 1H), 8.56 (t, 1H).

Reference example 3

4-fluoro-2-[N-(3-pyridylcarbonyl)amino]benzamide

[0102]



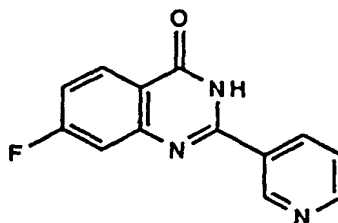
[0103] To a solution of the anthranilamide compound (1.54 g, prepared in Reference example 2) and triethylamine (1.4 g) in 100 mL of tetrahydrofuran was added nicotinoyl chloride hydrochloride (1.95 g). The resulting mixture was heated to reflux for one to three days and then concentrated. The residue was taken up in water (25 mL) and chloroform (30 mL). The insoluble crude product was collected by filtration and then vacuum dried. The crude product was triturated with 10 mL of ether and pentane solution (1:1) to afford the title compound (2.27 g) as a white solid having the following physical data.

NMR (200MHz, DMSO-d<sub>6</sub>): δ 7.10 (td, 1H), 7.80 (m, 1H), 7.99 (broad, 1H), 8.07 (m, 1H), 8.40-8.55 (m, 3H), 8.90 (m, 1H), 9.15 (m, 1H).

Reference example 4

7-fluoro-2-(3-pyridyl)quinazolin-4-one

[0104]



[0105] To a suspension of the benzamide compound (1.6 g, prepared in Reference example 3) in 60 mL of toluene was added sodium methoxide (853 mg). The solution was heated to reflux for one to three days. After cooling to room temperature, the mixture was quenched with ammonium chloride solution (30 mL) with a vigorously shaking. The mixture was cooled in refrigerator and the insoluble product was collected by filtration and dried in vacuum to give the title compound (1.39 g) as a white solid having the following physical data.

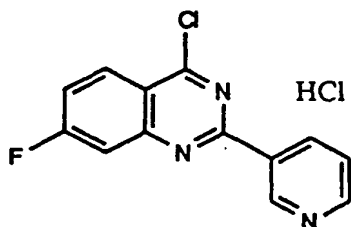
NMR (200MHz, DMSO-d<sub>6</sub>): δ 7.43 (td, 1H), 7.53-7.64 (m, 2H), 8.20-8.28 (m, 1H), 8.50 (dt, 1H), 8.78 (dd, 1H), 9.29 (m, 1H).



Reference example 5

4-chloro-7-fluoro-2-(3-pyridyl)quinazoline hydrochloride

[0106]



[0107] A suspension of the quinazolinone compound (1.2 g, prepared in Reference example 4) in 20 mL of thionyl chloride was heated to reflux for three hours. The excess of thionyl chloride was removed by distillation. The residue was distilled azeotropically with benzene (5 mL X 3) and then reduced the total volume to about 5 mL. After cooling in refrigerator, precipitate was collected by filtration and washed with benzene twice to give the title compound (1.38 g) as a crystalline solid having the following physical data.

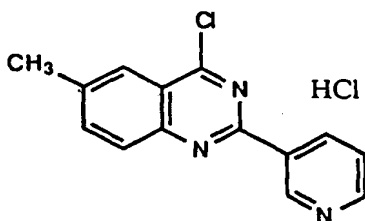
NMR (200MHz, DMSO-d6):  $\delta$  7.80-7.95 (m, 2H), 8.07 (dd, 1H), 8.43-8.49 (m, 1H), 8.95 (d, 1H), 9.06 (dt, 1H), 9.65 (m, 1H).

[0108] The following compounds were obtained by the same procedure as Reference example 3  $\rightarrow$  Reference example 4  $\rightarrow$  Reference example 5, by using the anthranilamide compound prepared in Reference example 2(a), 2(b) or 2(c), or being on sale, and the corresponding acid chloride.

Reference example 5(a)

4-chloro-6methyl-2-(3-pyridyl)quinazoline hydrochloride

[0109]



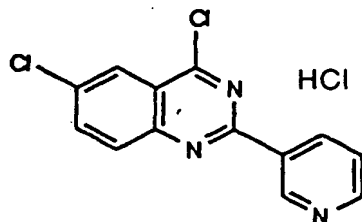
The product was collected by filtration as a white solid.

NMR (200MHz, DMSO-d6):  $\delta$  2.62 (s, 3H), 7.96-8.14 (m, 4H), 8.98 (d, 1H), 9.16 (d, 1H), 9.63 (m, 1H).

Reference example 5(b)

4,6-dichloro-2-(3-pyridyl)quinazoline hydrochloride

[0110]



The product was collected by filtration as a white solid.

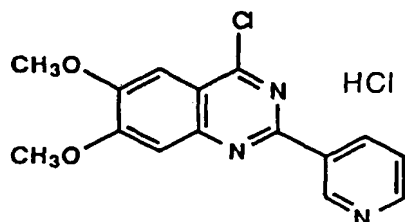
mp : 210-214 °C.

NMR (CDCl<sub>3</sub>): δ 7.28-8.17 (m, 3H), 8.35 (m, 1H), 8.89 (dd, 1H), 9.55 (dt, 1H), 9.98 (d, 1H).

Reference example 5(c)

4-chloro-6,7-dimethoxy-2-(3-pyridyl)quinazoline hydrochloride

[0111]



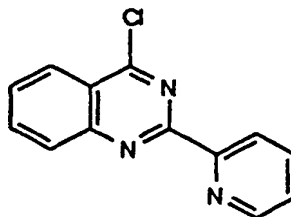
The product was collected by filtration as a white solid.

NMR (200MHz, DMSO-d<sub>6</sub>): δ 4.04 (s, 3H), 4.06 (s, 3H), 7.46 (s, 1H), 7.56 (s, 1H), 7.95 (m, 1H), 8.93 (d, 1H), 9.09 (d, 1H), 9.60 (m, 1H).

Reference example 5(d)

4-chloro-2-(2-pyridyl)quinazoline

[0112]



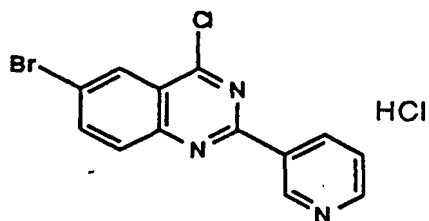
The product was collected by filtration as a light brown powder.

mp : 120-121 °C

Reference example 5(e)

6-bromo-4-chloro-2-(3-pyridyl)quinazoline hydrochloride

[0113]

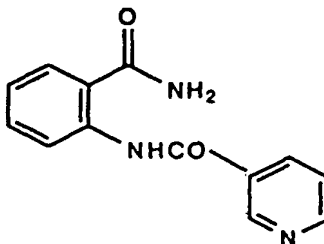


NMR (200MHz, DMSO-d<sub>6</sub>): δ 8.02 (m, 1 H), 8.14 (dd, 1 H), 8.33 (dt, 1 H), 8.50 (t, 1H), 9.01 (d, 1H), 9.14(d, 1H), 9.64 (t, 1H).

Reference example 6

2-[N-(3-pyridylcarbonyl)amino]benzamide

[0114]



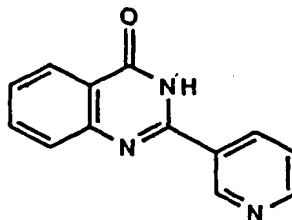
[0115] To a solution of anthranilamide (8.2 g, being on sale) and triethylamine (18.0 g) in 100 mL of tetrahydrofuran/ methylene chloride (1:1), was added nicotinoyl chloride hydrochloride (10.8 g). The mixture was allowed to stir at room temperature, under nitrogen atmosphere, for six hours. The solution was then concentrated under reduced pressure. The concentrate was taken up in ethyl acetate and water and the mixture filtered. The solid material was triturated in ether and filtered to give the title compound (11.5 g) as a yellow powder having the following physical data.

mp : 220-222 °C.

Reference example 7

2-(3-pyridyl)quinazolin-4-one

[0116]



[0117] To a solution of the benzamide compound (11.5 g, prepared in Reference example 6) in 100 mL of toluene was added 95% sodium methoxide (5.7 g). The solution was heated at 60-80° C for three hours under nitrogen atmosphere. After cooling to room temperature, the solution was diluted with ammonium chloride solution. After stirring for one-half hour, the mixture was filtered. An NMR of the filtered material indicated the reaction was incomplete. The material was taken up in toluene and ethanol and 95% sodium methoxide (5.7 g) was added. The resulting solution was heated to reflux and stirred via a mechanical stirrer, under nitrogen atmosphere, overnight. The solvent had evaporated and the concentrate in the flask was collected and washed with ammonium chloride solution and methylene chloride. The solid material was collected by filtration and allowed to dry to give the title compound as a gray powder having the following physical data.

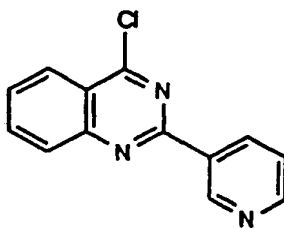
mp : 275-276 °C.

NMR (200MHz, DMSO-d<sub>6</sub>): δ 7.50-7.61 (m, 2H), 7.75-7.90 (m, 2), 8.16 (d, 1H), 8.49 (m, 1H), 8.77 (d, 1H), 9.31 (s, 1H). IR (KBr): ν 3185 (w), 3045 (m), 2915 (w), 1677 (s), 1603 (m), 1558 (w), 1474 (m), 769 (m) cm<sup>-1</sup>.

Reference example 8

4-chloro-2-(3-pyridyl)quinazoline

[0118]



[0119] A solution of the quinazolinone compound (6.7 g, prepared in Reference example 7) and 5.7 mL of N,N-dimethylaniline in 200 mL of benzene was heated to reflux, under nitrogen atmosphere, for one-half hour with the removal of 15 mL of distillate. After cooling to room temperature, phosphorus oxychloride (4.5 g) was added and the resulting solution heated to reflux for six hours. After cooling to room temperature, the solution was washed with ice water and dilute sodium hydroxide solution. The organic extract was dried over sodium sulfate and concentrated under reduced pressure. The concentrate was triturated in ether and collected to give the title compound (3.0 g) having the following physical data.

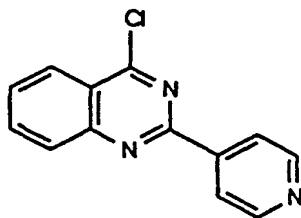
mp : 178-179 °C.

[0120] The following compounds were obtained by the same procedure as Reference example 6 → Reference example 7 → Reference example 8, by using anthranilamide and the corresponding acid chloride.

Reference example 8(a)

4-chloro-2-(4-pyridyl)quinazoline

[0121]

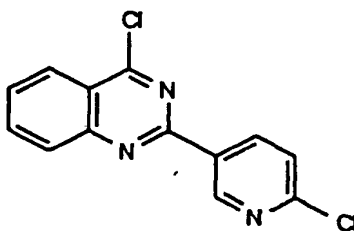


The product was collected by filtration as a brown solid.  
mp : 158-160°C

Reference example 8(b)

4-chloro-2-(2-chloro-5-pyridyl)quinazoline

[0122]

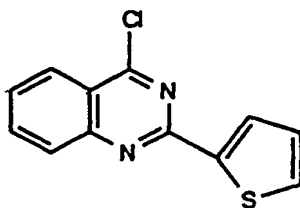


NMR (CDCl<sub>3</sub>): δ 7.47 (d, 1H), 7.73 (t, 1H), 7.95 (t, 1H), 8.05-8.32 (m, 2H), 8.81 (dd, 1H), 9.55 (ds, 1H).

Reference example 8(c)

4-chloro-2-(2-thienyl)quinazoline

[0123]

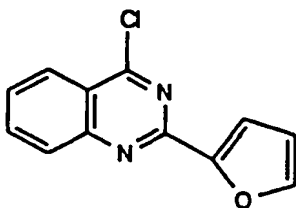


The product was collected by filtration as a tan powder.  
mp : 121-124 °C

Reference example 8(d)

4-chloro-2-(2-furyl)quinazoline

[0124]

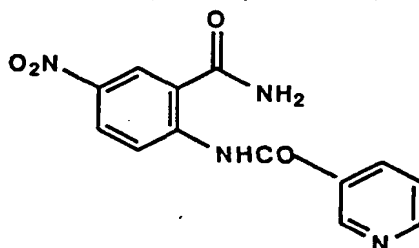


The product was collected by the filtration as a tan powder.  
mp : 116-119 °C

Reference example 9

5-nitro-2-[N-(3-pyridylcarbonyl)amino]benzamide

[0125]



[0126] The title compound was obtained by the same procedure as Reference example 3, by using 5-nitroanthranilamide (prepared in Reference example 2 (d)).

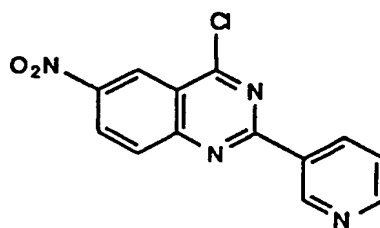
The product was collected by filtration as a white solid.

NMR (200MHz, DMSO-d6):  $\delta$  7.70 (m, 1H), 8.20 (broad, 1H), 8.35 (dt, 1H), 8.49 (dd, 1H), 8.85-8.92 (m, 3H), 9.15 (t, 1H).

Reference example 10

4-chloro-6-nitro-2-(3-pyridyl)quinazoline

[0127]



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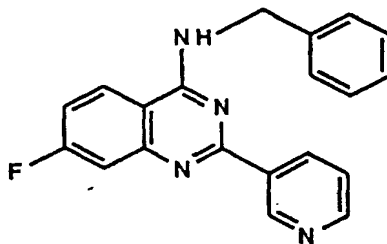
[0128] A suspension of the benzamide compound (0.925 g, prepared in Reference example 9) in phosphorous oxychloride (6 mL) was heated to reflux for 16 hours. After cooling to room temperature, the mixture was diluted by chloroform (30 mL) and then poured into 30 mL of ice-water mixture. The mixture was cooled in ice bath and carefully neutralized to pH 8 with a temperature control under 10 °C. The aqueous layer was extracted with chloroform (50 mL X 3). Combined organic layers were dried over with potassium carbonate and concentrated under reduced pressure to give the title compound (0.8 g) having the following physical data.

NMR (CDCl<sub>3</sub>): δ 7.27-7.35 (m, 2H), 7.52 (dd, 1H), 8.46-8.63 (m, 3H), 8.87 (d, 1H), 9.42 (s, 1H).

### Example 1

4-phenylmethylamino-7-fluoro-2-(3-pyridyl)quinazoline

[0129]



[0130] To a warm solution of the 4-chloroquinazoline compound (1.18 g, prepared in Reference example 5) in 50 mL ethanol was added phenylmethylamine (2.00 g). The mixture was heated to reflux for sixteen hours. The solution was then concentrated and the residue taken up in chloroform and ammonium chloride solution. The aqueous layer was extracted with chloroform (30 mL X 3) and dried over sodium sulfate. After concentration, the residue was triturated in pentane/ether solution to give the title compound (0.88 g) as a pale white solid having the following physical data. mp : 199-203 °C.

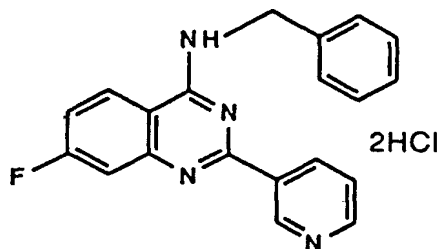
NMR (CDCl<sub>3</sub>): δ 5.00 (d, 2H), 6.01 (broad, 1H), 7.20 (td, 1H), 7.25-7.50 (m, 6H), 7.55 (dd, 1H), 7.70-7.77 (m, 1H), 8.70 (dd, 1H), 8.79 (dt, 1H), 9.74 (m, 1H).

IR (KBr): ν 697 (s), 775 (s), 1166 (m), 1259 (m), 1341 (s), 1375 (s), 1444 (s), 1535 (s), 1592 (s), 1626 (s), 3135 (m), 3250 (m) cm<sup>-1</sup>.

### Example 2

4-phenylmethylamino-7-fluoro-2-(3-pyridyl)quinazoline dihydrochloride

[0131]



[0132] To a suspension of the free base (0.70 g, prepared in Example 1) in 10 ml methanol was added excess amount of HCl in methanol. The mixture was stirred at room temperature for a half of an hour. The solvent was removed and the residue was triturated in ether (30 ml). The title compound (0.84 g) as a white powder having the following physical data, was obtained after filtration.

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mp : 250 °C.

NMR (CDCl<sub>3</sub>): δ 4.50 (d, 2H), 7.25-7.40 (m, 3H), 7.49-7.53 (m, 2H), 7.64 (dt, 1H), 7.82 (dd, 1H), 7.99 (m, 1H), 8.67 (m, 1H), 8.97 (dd, 1H), 9.15 (dd, 1H), 9.60 (d, 1H), 10.18 (broad, 1H).

IR (KBr): ν 704 (m), 1266 (m), 1457 (s), 1574 (s), 1632 (s), 2920-2440 (broad, s), 3115 (broad, s) cm<sup>-1</sup>.

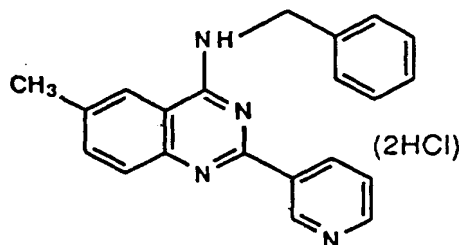
Example 3

[0133] The following compounds were obtained by the same procedure as Example 1, or Example 1 and Example 2, by using the corresponding 4-chloroquinazoline compound prepared by Reference example 5, 5(a) to 5(e) or Reference example 8, 8(a) to 8(d) and the proper amine.

Example 3(a)

4-phenylmethylamino-6-methyl-2-(3-pyridyl)quinazoline and its salt

[0134]



(free base)

The product was collected by filtration as a white solid.

mp: 179-180 °C (dec.).

NMR (CDCl<sub>3</sub>): δ 5.03 (d, 2H), 5.97 (broad, 1H), 7.28-7.53 (m, 7H), 7.61 (dd, 1H), 7.86 (d, 1H), 8.69 (dd, 1H), 8.80 (dt, 1H), 9.76 (m, 1H).

IR (KBr): ν 699 (w), 1365 (m), 1407 (w), 1437 (w), 1535 (s), 1569 (s), 1591 (s), 3200 (m) cm<sup>-1</sup>.

(2HCl salt)

The product was collected by filtration as a white powder.

mp : 265-269 °C (dec.).

NMR (CDCl<sub>3</sub>): δ 2.50 (s, 3H), 5.03 (d, 2H), 7.28-7.42 (m, 3H), 7.48-7.53 (m, 2H), 7.80-7.91 (m, 2H), 8.06 (d, 1H), 8.45 (s, 1H), 8.91-9.00 (m, 2H), 9.55 (m, 1H).

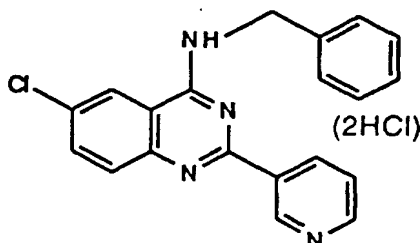
IR (KBr): ν 704 (w), 1388 (m), 1568 (s), 1593 (s), 1617 (s), 2400-3100 (broad, s), 3200 (m), 3410 (broad, m) cm<sup>-1</sup>.



Example 3(b)

4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline and its salt

[0135]



(free base)

The product was purified by column chromatography.

mp : 240 °C.

NMR (CDCl<sub>3</sub>): δ 5.00 (d, 2H), 5.92 (broad, 1H), 7.32-7.51 (m, 6H), 7.71 (m, 2H), 7.90 (d, 1H), 8.71 (dd, 1H), 8.79 (dt, 1H), 9.75 (d, 1H).IR (KBr): ν 697 (m), 1368 (s), 1419 (m), 1439 (m), 1534 (s), 1568 (s), 1590 (s), 3260 (w) cm<sup>-1</sup>.

(2HCl salt)

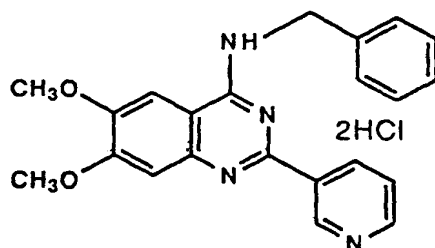
The product was collected by filtration as a white powder.

mp : 255 °C (dec.).

NMR (CDCl<sub>3</sub>): δ 4.99 (d, 2H), 7.25-7.42 (m, 3H), 7.45-7.55 (m, 2H), 7.96-8.10 (m, 3H), 8.72 (m, 1H), 8.96 (d, 1H), 9.15 (d, 1H), 9.60 (m, 1H).IR (KBr): ν 671 (w), 709 (m), 1356 (m), 1387 (s), 1457 (m), 1488 (m), 1518 (m), 1569 (s), 1608 (s), 1631 (s), 2335-2890 (broad, s), 3825 (s), 3230 (m), 3425 (m) cm<sup>-1</sup>.Example 3(c)

4-phenylmethylamino-6,7-dimethoxy-2-(3-pyridyl)quinazoline and its salt

[0136]



(free base)

The product was collected by filtration as a white solid.

mp : 193-196 °C.

NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.92 (s, 3H), 3.94 (s, 3H), 4.92 (d, 2H), 6.90 (broad, 1H), 7.23-7.38 (m, 4H), 7.46-7.55 (m, 3H), 7.76 (s, 1H), 8.62-8.78 (m, 3H), 9.52 (m, 1H).IR (KBr): ν 698 (m), 850 (m), 1026 (m), 1131 (m), 1183 (m), 1213 (s), 1243 (s), 1366 (s), 1450 (s), 1501 (s), 1528 (s), 1591 (s), 1622 (m), 3270 (w) cm<sup>-1</sup>.

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(2HCl salt)

The product was collected by filtration as a white solid.

mp : 240 °C (dec.).

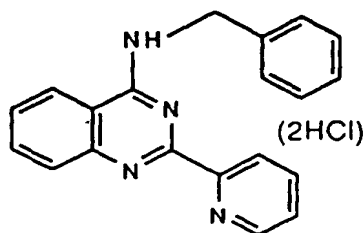
NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.98 (s, 6H), 5.01-5.06 (m, 2H), 7.25-7.41 (m, 3H), 7.74 (s, 1H), 7.85 (m, 1H), 8.14 (s, 1H), 8.90-8.95 (m, 2H), 9.56 (m, 1H).

IR (KBr): ν 1243 (w), 1287 (s), 1378 (m), 1473 (m), 1504 (s), 1542 (m), 1596 (m), 1634 (s), 2400-3200 (broad, s), 3440 (broad, s) cm<sup>-1</sup>.

Example 3(d)

4-phenylmethylamino-2-(2-pyridyl)quinazoline and its salt

[0137]



(free base):

The product was collected by filtration as a tan solid.

mp : 165-169 °C

(2HCl salt)

mp : 140-155 °C

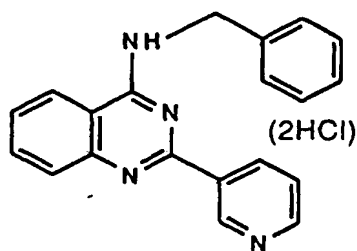
NMR (200MHz, DMSO-d<sub>6</sub>): δ 5.12 (d, 2H), 7.35 (m, 3H), 7.58 (d, 2H), 7.83 (qd, 2H), 8.07 (t, 1H), 8.19-8.36 (m, 2H), 8.64 (d, 1H), 8.82 (d, 1H), 8.93 (d, 1H), 11.40 (t, 1H).

IR (KBr): ν 3370 (m), 3220 (m), 3200-2700 (m), 1625 (s), 1562 (s), 1524 (m), 1466 (m), 1385 (m), 765 (m) cm<sup>-1</sup>.

Example 3(e)

4-phenylmethylamino-2-(3-pyridyl)quinazoline and its salt

[0138]



(free base)

mp : 137-138 °C.

NMR (CDCl<sub>3</sub>): δ 5.01 (d, 2H), 6.20 (t, 1H), 7.26-7.49 (m, 6H), 7.71-7.79 (t, 3H), 7.95 (d, 1H), 8.68 (bs, 1H), 8.82 (d, 1H), 9.75 (bs, 1H).

IR (KBr): ν 3305 (m), 1584 (s), 1520 (s), 1437 (m), 1410 (m), 1365 (s), 1325 (w), 765 (m), 694 (m) cm<sup>-1</sup>.

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(2HCl salt)

mp : 225-235 °C

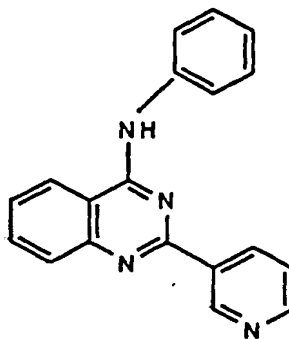
NMR (200MHz, DMSO-d<sub>6</sub>):  $\delta$  5.05 (d, 2H), 7.22-7.43 (m, 3H), 7.52 (m, 2H), 7.78 (t, 1H), 7.94-8.13 (m, 2H), 8.36 (s, 1H), 8.78 (d, 1H), 9.00 (dd, 1H), 9.12 (dd, 1H), 9.70 (s, 1H), 11.16 (broad t, 1H).

IR (KBr):  $\nu$  3300-2615 (broad,s), 1629 (s), 1605 (s), 1569 (s), 1456 (m), 1384 (m), 763 (m), 705 (m) cm<sup>-1</sup>.

Example 3(f)

4-phenylamino-2-(3-pyridyl)quinazoline

[0139]



The product was collected by filtration as a yellow powder.

mp :173-178 °C.

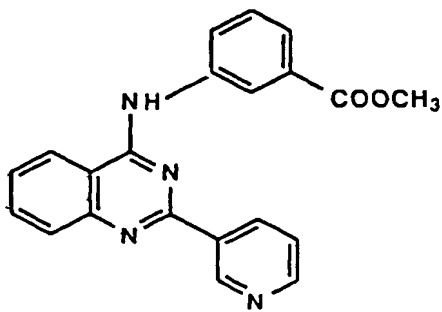
NMR (200MHz, DMSO-d<sub>6</sub>):  $\delta$  7.29 (t, 1H), 7.53 (t, 2H), 7.72-8.17 (m, 6H), 8.80 (d, 1H), 8.93 (d, 1H), 9.05 (d, 1H), 9.52 (s, 1H), 10.81 (bs, 1H).

IR (KBr):  $\nu$  3160 (bw), 1559 (s), 1520 (s), 1411 (m), 1363 (m), 754 (m) cm<sup>-1</sup>.

Example 3(g)

4-(3-methoxycarbonylphenyl)amino-2-(3-pyridyl)quinazoline

[0140]



The product was collected by filtration as a yellow powder.

mp : 228-245 °C.

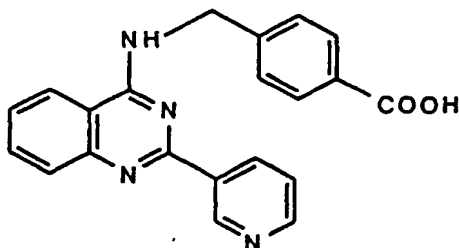
NMR (200MHz, DMSO-d<sub>6</sub>):  $\delta$  3.94 (s, 3H), 7.56-8.04 (m, 7H), 8.72-9.08 (m, 4H), 9.57 (s, 1H), 10.61 (bs, 1H).

IR (KBr):  $\nu$  3400 (bw), 1717(m), 1562 (s), 1520 (m), 1447 (m), 1374 (m), 1299 (m), 1278(m), 752 (m), 672 (w) cm<sup>-1</sup>.

Example 3(h)

4-(4-carboxyphenylmethyl)amino-2-(3-pyridyl)quinazoline

[0141]



mp : 285-294 °C

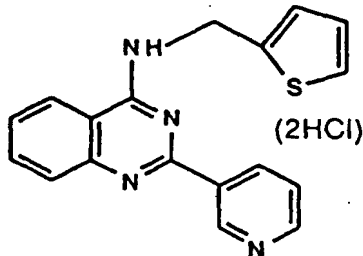
NMR (200MHz, DMSO-d<sub>6</sub>): δ 4.98 (d, 2H), 7.50-7.62 (m, 4H), 7.81 (d, 2H), 7.90 (d, 2H), 8.37 (d, 1H), 8.65 (m, 2H), 9.13 (t, 1H), 9.49 (s, 1H).

IR (KBr): ν 3340 (broad), 1.747 (m), 1586 (s), 1531 (s), 1366 (m), 765 (m) cm<sup>-1</sup>.

Example 3(i)

4-(2-thienylmethyl)amino-2-(3-pyridyl)quinazoline and its salt

[0142]



(free base)

mp : 195-197 °C

NMR (200MHz, DMSO-d<sub>6</sub>): δ 5.08 (d, 2H), 6.99 (m, 1H), 7.19 (m, 1H), 7.35 (dd, 1H), 7.55 (m, 2H), 8.30 (s, 1H), 8.69 (m, 1H), 8.83 (m, 1H), 9.13 (t, 1H).

IR (KBr): ν 3260 (bw), 1583 (s), 1525 (s), 1449 (m), 1359 (s), 763 (m), 747 (m), 720 (m) cm<sup>-1</sup>.

(2HCl salt)

mp : 255 °C (dec.).

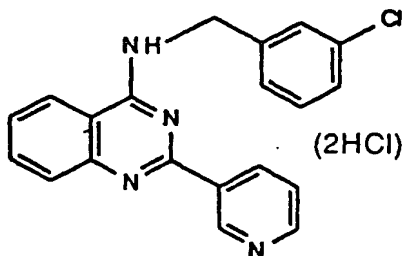
NMR (200MHz, DMSO-d<sub>6</sub>): δ 5.20 (d, 2H), 7.01 (m, 1H), 7.22 (m, 1H), 7.43 (s, 1H), 7.77 (t, 1H), 8.00 (m, 3H), 8.21 (d, 1H), 8.61 (d, 1H), 8.99 (d, 1H), 9.23 (d, 1H), 9.74 (s, 1H), 10.45 (bs, 1H).

IR (KBr): ν 3405 (w), 3060-2615 (broad, m), 2363 (w), 1631 (s), 1608 (s), 1570 (s), 1458 (m), 1387 (m), 773 (m), 712 (m) cm<sup>-1</sup>.

Example 3(j)

4-(3-chlorophenylmethyl)amino-2-(3-pyridyl)quinazoline and its salt

[0143]



(free base)

mp : 203-205 °C

NMR (200MHz, DMSO-d6):  $\delta$  4.92 (d, 2H), 7.27-7.61 (m, 6H), 7.82 (d, 2H), 8.33 (d, 1H), 8.66 (m, 2H), 9.08 (t, 1H), 9.53 (s, 1H).IR (KBr):  $\nu$  3245 (w), 3050-2800 (w), 1586 (s), 1533 (m), 1436 (w), 1412 (w), 1366 (m), 765 (w)  $\text{cm}^{-1}$ .

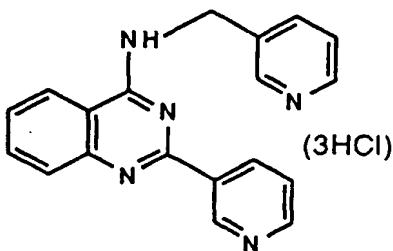
(2HCl salt)

mp : 235-250 °C

NMR (200MHz, DMSO-d6):  $\delta$  5.05 (d, 2H), 7.35 (m, 2H), 7.49 (m, 1H), 7.62 (s, 1H), 7.78 (t, 1H), 7.90-8.12 (m, 2H), 8.28 (s, 1H), 8.97 (m, 1H), 9.13 (dd, 1H), 9.66 (s, 1H), 10.97 (bs, 1H).IR (KBr):  $\nu$  3035 (m), 2900-2700 (m), 1634 (m), 1610 (m), 1569 (m), 1387 (w), 780 (w), 710 (w)  $\text{cm}^{-1}$ .Example 3(k)

4-(3-pyridylmethyl)amino-2-(3-pyridyl)quinazoline and its salt

[0144]



(free base)

mp : 157-161 °C

NMR (200MHz, DMSO-d6):  $\delta$  4.95 (d, 2H), 7.33 (m, 1H), 7.55 (m, 2H), 7.85 (m, 3H), 8.33 (d, 1H), 8.46 (dd, 1H), 8.65-8.76 (m, 3H), 9.10 (t, 1H), 9.57 (s, 1H).IR (KBr):  $\nu$  3255 (m), 3050-2900 (w), 1586 (s), 1533 (s), 1438 (m), 1368 (s), 763 (m), 700 (m)  $\text{cm}^{-1}$ .

(3HCl salt)

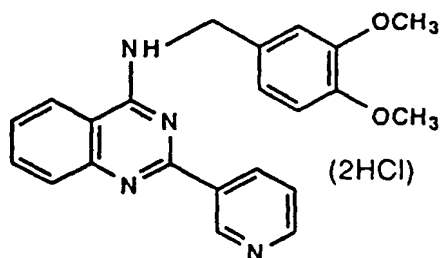
mp : 240-257 °C

NMR (200MHz, DMSO-d6):  $\delta$  5.25 (d, 2H), 7.77 (t, 1H), 8.07 (m, 2H), 8.29 (d, 1H), 8.83 (m, 4H), 9.00 (d, 1H), 9.19 (m, 2H), 9.69 (s, 1H), 11.25 (bs, 1H).IR (KBr):  $\nu$  3500 (w), 3100-2500 (broad, m), 1633 (s), 1611(s), 1569 (m), 1542 (m), 1457 (w), 790 (w), 720 (w)  $\text{cm}^{-1}$ .

Example 3(l)

4-(3,4-dimethoxyphenylmethyl)amino-2-(3-pyridyl)quinazoline and its salt

[0145]



(free base)

mp : 155-159 °C

NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.71 (d, 6H), 4.85 (d, 2H), 6.83-7.05 (m, 2H), 7.18 (s, 1H), 7.54 (m, 2H), 7.82 (d, 2H), 8.32 (d, 1H), 8.68 (dd, 1H), 8.77 (dd, 1H), 9.01 (t, 1H), 9.63 (s, 1H).IR (KBr): ν 3395 (w), 3200-2900 (w), 1584 (s), 1514 (s), 1364 (m), 1263 (m), 1025 (m), 764 (w) cm<sup>-1</sup>.

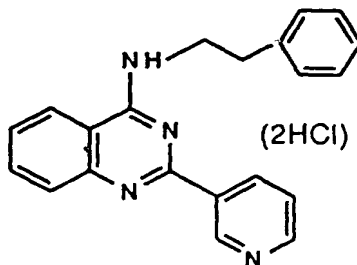
(2HCl salt)

mp : 215-220 °C

NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.70 (s, 6H), 4.97 (d, 2H), 6.90 (d, 1H), 7.02 (d, 1H), 7.24 (s, 1H), 7.77 (t, 1H), 7.92 (m, 1H), 8.04 (t, 1H), 8.73 (d, 1H), 8.97 (d, 1H), 9.16 (dd, 1H), 9.70 (s, 1H), 10.94 (bs, 1H).IR (KBr): ν 3404 (m), 3200-2300 (m), 1631 (s), 1610 (s), 1569 (s), 1514 (s), 1264 (m), 765 (m) cm<sup>-1</sup>.Example 3(m)

4-phenylethylamino-2-(3-pyridyl)quinazoline and its salt

[0146]



(free base)

mp : 136-139 °C

NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.07 (t, 2H), 3.89 (q, 2H), 7.20-7.30 (m, 3H), 7.32 (d, 2H), 7.55 (m, 2H), 7.82 (s, 2H), 8.26 (s, 1H), 8.59 (t, 1H), 8.70 (m, 2H), 9.65 (s, 1H).IR (KBr): ν 3290 (m), 3050-2900 (w), 1591 (s), 1514 (s), 1534 (s), 1442 (m), 1370 (s), 761 (m), 702 (m) cm<sup>-1</sup>.

(2HCl salt)

mp : 220-250°C (dec.).

NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.11 (t, 2H), 4.05 (q, 2H), 7.15-7.38 (m, 5H), 7.77 (t, 1H), 8.01 (m, 2H), 8.35 (d, 1H), 8.70 (d, 1H), 9.01 (d, 1H), 9.15 (d, 1H), 9.69 (s, 1H), 10.68 (bs, 1H).

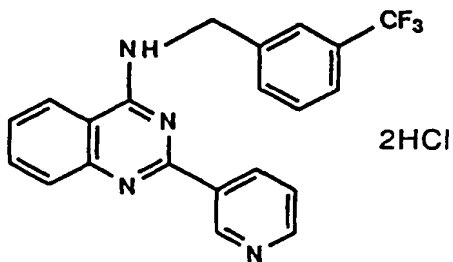
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IR (KBr):  $\nu$  3400 (w), 3100-2500 (m), 1633 (s), 1613 (s), 1570 (m), 1457 (m), 1385 (m), 790 (w), 720 (w)  $\text{cm}^{-1}$ .

Example 3(n)

4-(3-trifluoromethylphenylmethyl)amino-2-(3-pyridyl)quinazoline dihydrochloride

[0147]



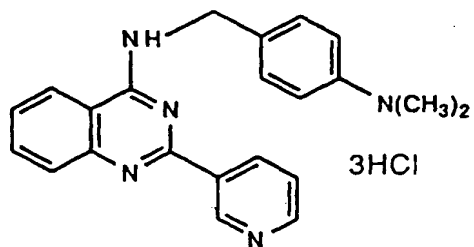
mp :  $>280\text{ }^{\circ}\text{C}$

NMR (200MHz, DMSO- $d_6$ ):  $\delta$  5.14 (d, 2H), 7.52-8.35 (m, 8H), 8.70-9.20 (m, 3H), 9.67 (m, 1H).

Example 3(o)

4-(4-(N,N-dimethylamino)phenylmethyl)amino-2-(3-pyridyl)quinazoline trihydrochloride

[0148]



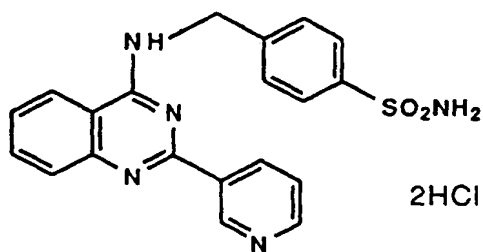
mp :  $200-250\text{ }^{\circ}\text{C}$  (dec.).

NMR (200MHz, DMSO- $d_6$ ):  $\delta$  3.04 (s, 6H), 5.05 (d, 2H), 7.50-8.30 (m, 8H), 8.72 (s, 1H), 8.92-9.12 (m, 2H), 9.60 (m, 1H).

Example 3(p)

4-(4-sulfamoylphenylmethyl)amino-2-(3-pyridyl)quinazoline dihydrochloride

[0149]



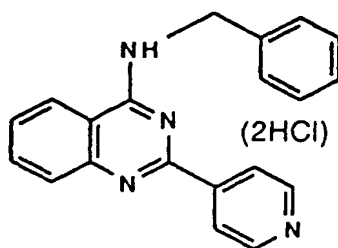
mp : 255-265 °C

NMR (200MHz, DMSO-d6):  $\delta$  5.10 (d, 2H), 7.32 (bs, 2H), 7.66-8.20 (m, 8H), 8.62 (d, 1H), 8.95 (m, 2H), 9.56 (ms, 1H).

Example 3(q)

4-phenylmethylamino-2-(4-pyridyl)quinazoline and its salt

[0150]



(free base)

mp : 195-197 °C

NMR (200MHz, DMSO-d6):  $\delta$  4.96 (d, 2H), 7.19-7.66 (m, 6H), 7.83 (d, 2H), 8.30 (d, 2H), 8.39 (d, 1H), 8.72 (d, 2H), 9.10 (t, 1H).

IR (KBr):  $\nu$  3250 (w), 1585 (s), 1561 (s), 1529 (s), 1411 (m), 1374 (s), 1325 (s), 768 (m), 702 (m)  $\text{cm}^{-1}$ .

(2HCl salt):

mp : 260-270 °C

NMR (200MHz, DMSO-d6):  $\delta$  5.02 (d, 2H), 7.22-7.40 (m, 3H), 7.51 (d, 2H), 7.75 (t, 1H), 8.00 (t, 1H), 8.16 (d, 1H), 8.66 (d, 1H), 8.81 (d, 2H), 9.06 (d, 2H), 10.32 (bs, 1H).

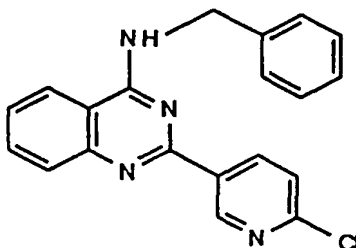
IR (KBr):  $\nu$  3385 (m), 3210 (m), 3060-2600 (s), 1627 (s), 1604 (s), 1567 (s), 1505 (m), 1452 (m), 1383 (m), 760 (m), 709 (m)  $\text{cm}^{-1}$ .



Example 3(s)

4-phenylmethylamino-2-(2-chloro-5-pyridyl)quinazoline

[0151]

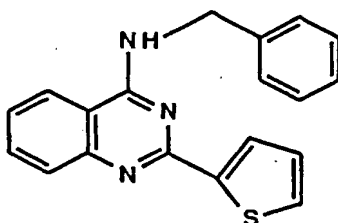


mp : 212-214 °C

NMR (CDCl<sub>3</sub>): δ 4.96 (d, 2H), 6.03 (bs, 1H), 7.20-7.55 (m, 7H), 7.66-7.95 (m, 3H), 8.78 (m, 1H), 9.52 (m, 1H).IR (KBr): ν 3315 (w), 1580 (s), 1532 (ms), 1446 (mw), 1343 (m), 1269 (w) cm<sup>-1</sup>.Example 3(t)

4-phenylmethylamino-2-(2-thienyl)quinazoline

[0152]

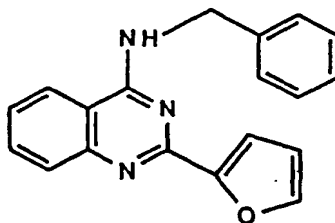


mp : 158-163 °C

NMR (200MHz, DMSO-d<sub>6</sub>): δ 4.88 (d, 2H), 7.14-7.53 (m, 6H), 7.62-7.81 (m, 3H), 7.92 (m, 1H), 8.30 (d, 1H), 8.97 (t, 1H).IR (KBr): ν 3305 (w), 1571 (s), 1519 (s), 1451 (m), 1408 (m), 1377 (s), 769 (m), 730 (m), 737 (m) cm<sup>-1</sup>.Example 3(v)

4-phenylmethylamino-2-(2-furyl)quinazoline

[0153]



mp : 152-154 °C

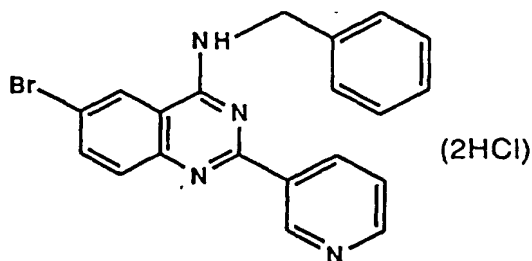
## EP 0 579 496 B1

NMR (CDCl<sub>3</sub>):  $\delta$  4.95 (d, 2H), 6.00 (t, 1H), 6.56 (m, 1H), 7.31-7.49 (m, 7H), 7.62-7.76 (m, 3H), 7.97 (d, 1H).  
IR (KBr):  $\nu$  3290 (m), 1589 (m), 1531(s), 1365 (s), 1015 (m), 890 (m), 762 (s) cm<sup>-1</sup>.

### Example 3(y)

4-phenylmethylamino-6-bromo-2-(3-pyridyl)quinazoline and its salt

[0154]



(free base)

The product was collected by filtration as a solid.

NMR (200MHz, DMSO-d<sub>6</sub>):  $\delta$  4.90 (d, 2H), 7.25-7.56 (m, 6H), 7.75 (d, 2H), 7.94 (dd, 1H), 8.66-8.71 (m, 3H), 9.18 (broad, 1H), 9.54 (d, 1H).

(2HCl salt)

mp : 233-240 °C (dec.).

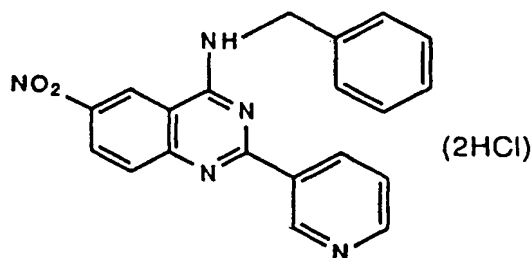
NMR (200MHz, DMSO-d<sub>6</sub>):  $\delta$  4.99 (d, 2H), 7.25-7.42 (m, 3H), 7.51-7.57 (m, 3H), 7.96-8.03 (m, 1H), 8.07-8.10 (m, 2H), 8.93-9.00 (m, 2H), 9.19 (d, 1H), 9.62 (d, 1H), 10.30 (broad, 1H).

IR (KBr):  $\nu$  701 (m), 1357 (m), 1404 (s), 1446 (m), 1519 (s), 1549 (s), 1628 (s), 2400-3000 (broad, s), 3140 (s) cm<sup>-1</sup>.

### Example 3(z)

4-phenylmethylamino-6-nitro-2-(3-pyridyl)quinazoline and its salt

[0155]



(free base)

The product was collected by filtration as a solid.

NMR (200MHz, DMSO-d<sub>6</sub>):  $\delta$  4.95 (d, 2H), 7.25-7.40 (m, 3H), 7.48-7.58 (m, 3H), 7.93 (dd, 1H), 8.50 (dt, 1H), 8.70-8.80 (m, 2H), 9.46 (d, 1H), 9.58 (d, 1H), 9.70 (broad, 1H).

(2HCl salt)

mp : 289-292 °C (dec.).

NMR (200MHz, DMSO-d<sub>6</sub>):  $\delta$  5.00 (d, 2H), 7.25-7.42 (m, 3H), 7.51-7.55 (m, 2H), 8.04-8.09 (m, 2H), 8.59 (dt, 1H),

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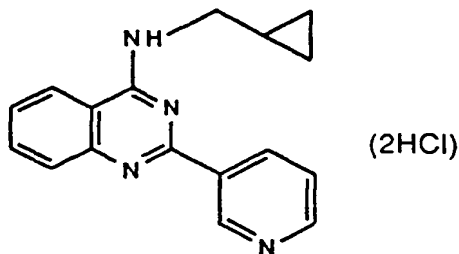
9.00 (dd, 1H), 9.27 (d, 1H), 9.54 (d, 1H), 9.67 (s, 1H), 10.18 (broad, 1H).

IR (KBr):  $\nu$  671 (m), 709 (m), 757 (m), 784 (m), 1349 (s), 1514 (s), 1578 (s), 1636 (s), 2445 (broad, s), 2860 (w), 3070 (m)  $\text{cm}^{-1}$ .

Example 3(aa)

4-(cyclopropylmethyl)amino-2-(3-pyridyl)quinazoline and its salt

[0156]



(free base)

mp : 162-163 °C.

NMR (200MHz, DMSO-d<sub>6</sub>):  $\delta$  0.38 (m, 2H), 0.49 (m, 2H), 1.33 (m, 1H), 3.58 (t, 2H), 7.55 (m, 2H), 7.79 (m, 2H), 8.32 (d, 1H), 8.56 (t, 1H), 8.69 (m, 2H), 9.62 (s, 1H).

IR (KBr):  $\nu$  3265(w), 1537 (s), 1525 (s), 1437 (w), 1369 (s), 762 (m)  $\text{cm}^{-1}$ .

(2HCl salt)

mp : 230-239 °C

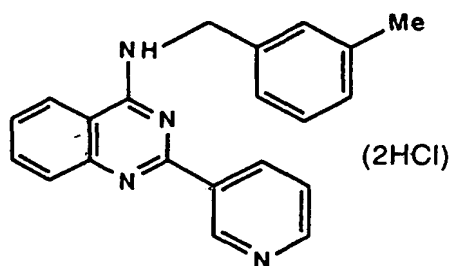
NMR (200MHz, DMSO-d<sub>6</sub>):  $\delta$  0.43 (m, 2H), 0.50 (m, 2H), 1.32 (m, 1H), 3.71 (t, 2H), 7.78 (t, 1H), 7.93 (m, 1H), 8.05 (t, 1H), 8.34 (d, 1H), 8.77 (d, 1H), 8.99 (d, 1H), 9.08 (dd, 1H), 9.68 (s, 1H), 10.68 (bs, 1H).

IR (KBr):  $\nu$  3405-2700 (broad, s), 2365 (w), 1632 (s), 1600 (s), 1570 (m), 1542 (m), 1458 (w), 1383 (m), 1321 (w), 767 (w), 669 (w)  $\text{cm}^{-1}$ .

Example 3(bb)

4-(3-methylphenylmethyl)amino-2-(3-pyridyl)quinazoline and its salt

[0157]



(free base)

mp : 166-169 °C.

NMR (200MHz, DMSO-d<sub>6</sub>):  $\delta$  2.28 (s, 3H), 4.90 (s, 2H), 7.03 (bd, 1H), 7.18-7.32 (m, 3H), 7.47-7.61 (m, 2H), 7.81 (d, 1H), 8.35 (d, 1H), 8.69 (m, 2H), 9.02 (bt, 1H), 9.58 (s, 1H).

IR (KBr):  $\nu$  3245 (m), 1567 (s), 1533 (s), 1438 (m), 1443 (m), 1368 (s), 1326 (m), 762 (m), 699 (m)  $\text{cm}^{-1}$ .

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(2HCl salt)

mp : 225-244 °C.

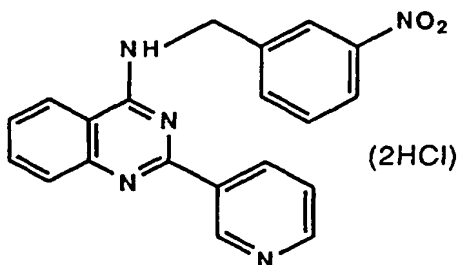
NMR (200MHz, DMSO-d6):  $\delta$  2.29 (s, 3H), 5.03 (s, 2H), 7.10 (d, 1H), 7.20-7.38 (m, 3H), 7.77 (t, 1H), 7.92-8.10 (m, 2H), 8.34 (d, 1H), 8.76 (d, 1H), 9.02 (d, 2H), 9.20 (d, 2H), 9.69 (s, 1H), 11.05 (bt, 1H).

IR (KBr):  $\nu$  3400 (m), 3050-2600 (broad, m), 1627 (s), 1570 (s), 1542 (m), 1457 (m), 1385 (m), 770 (m), 680 (m)  $\text{cm}^{-1}$ .

Example 3(dd)

4-(3-nitrophenylmethyl)amino-2-(3-pyridyl)quinazoline and its salt

[0158]



(free base)

mp : 218-220 °C.

NMR (200MHz, DMSO-d6):  $\delta$  5.05 (d, 2H), 7.46-7.69 (m, 3H), 7.83 (m, 2H), 7.84 (d, 1H), 8.13 (d, 1H), 8.37 (m, 2H), 8.67 (m, 2H), 9.18 (t, 1H), 9.52 (s, 1H).

(2HCl salt)

mp : 263-265 °C.

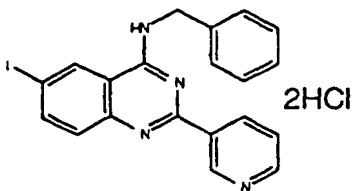
NMR (200MHz, DMSO-d6):  $\delta$  5.15 (d, 2H), 7.60-7.86 (m, 3H), 7.90-8.19 (m, 5H), 8.26 (d, 1H), 8.43 (s, 1H), 8.75 (d, 1H), 9.00 (d, 1H), 9.18 (d, 1H), 9.65 (s, 1H), 11.03 (bs, 1H).

[0159] The following compounds were obtained by the same procedure as described in Reference examples 2, 3, 4 and 5 and examples 1 and 2 or in Reference example 6, 7 and 8 and examples 1 and 2, by using isatoic anhydride.

Example 3(ff)

6-iodo-4-phenylmethylamino-2-(3-pyridyl)quinazoline dihydrochloride

[0160]



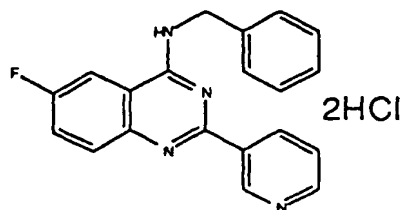
mp : 205-10 °C, (dec.)

NMR (200MHz, DMSO-d6)  $\delta$ : 5.00 (d, 2H), 7.28-7.41 (m, 3H), 7.47-7.53 (m, 2H), 7.80 (d, 1H), 7.95 (m, 1H), 8.23 (dd, 1H), 8.92-8.98 (m, 2H), 9.08 (d, 1H), 9.59 (m, 1H), 10.00 (broad, 1H).

Example 3(gg)

6-fluoro-4-phenylmethylamino-2-(3-pyridyl)quinazoline dihydrochloride

[0161]



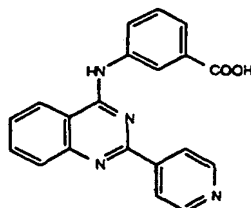
mp : 200-2 °C, (dec.)

NMR (200MHz, DMSO-d6)  $\delta$ : 5.02 (d, 2H), 7.28-7.41 (m, 3H), 7.51-7.54 (m, 2H), 7.82-8.02 (m, 2H), 8.07-8.20 (m, 1H), 8.40-8.52 (d, 1H), 8.97 (dd, 1H), 9.15 (d, 1H), 9.61 (s, 1H), 10.08 (broad, 1H).

Example 3(hh)

4-(3-carboxyphenyl)amino-2-(4-pyridyl)quinazoline

[0162]



mp : >300 °C

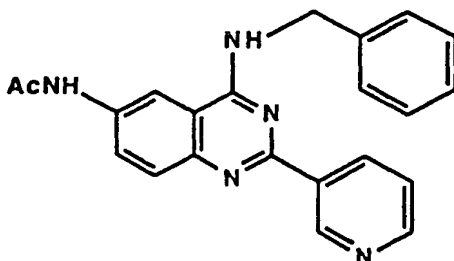
NMR (200MHz, DMSO-d6)  $\delta$ : 7.65 (t, 1H), 7.78 (m, 2H), 7.99 (d, 2H), 8.22 (d, 1H), 8.68 (d, 2H), 8.75 (d, 1H), 8.87 (m, 3H), 10.44 (s, 1H).

IR (KBr)  $\nu$ : 3370-2800 (w, broad), 1712 (m), 1632 (m), 1571 (s), 1545 (s), 1473 (m), 1437 (m), 1376 (m), 764 (m)  $\text{cm}^{-1}$ .

Example 4

6-acetylamino-4-phenylmethylamino-2-(3-pyridyl)quinazoline

[0163]



[0164] To warmed suspension of the nitroquinazoline compound (141 mg, prepared in Example 3(z)) in acetic acid (4 mL) was added zinc dust (80 mg). The red mixture was heated to reflux for overnight. After cooling down to room temperature the precipitate was removed by filtration. The filtrate was neutralized to pH 8 and extracted with chloroform. The insoluble solid was removed by filtration during the extraction. The chloroform was dried over potassium carbonate and then concentrated to 0.5 mL (total volume). The precipitate was collected by filtration to give the title compound (20 mg) having the following physical data.

mp : 127 °C (dec.).

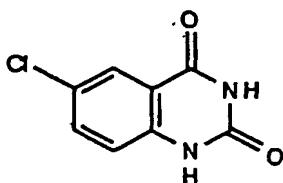
NMR (200MHz, DMSO-d<sub>6</sub>): δ 2.12 (s, 3H), 4.88 (d, 2H), 7.22-7.37 (m, 3H), 7.45-7.53 (m, 2H), 7.75 (m, 1H), 8.32 (m, 2H), 8.58-8.69 (m, 3H), 8.94 (broad, 1H), 9.52 (m, 1H), 10.23 (broad, 1H).

IR (KBr): ν 700 (w), 840 (w), 1318 (m), 1368 (m), 1426 (m), 1537 (s), 1584 (s), 1676 (m), 3065 (m), 3365 (m) cm<sup>-1</sup>.

Reference example 11

6-chloro-(1 H,3H)-quinazolin-2,4-dione

[0165]



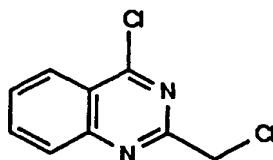
[0166] To a solution of 5-chloroanthranilamide (3.4 g) in tetrahydrofuran (50 mL) was added phosgene (16 mL, 1.93M solution in toluene) via an addition funnel. The reaction mixture was stirred at room temperature for 4 hours and then heated to reflux for another two hours. The reaction mixture was concentrated to a total volume about 10 mL. After cooling, the title compound (3.72 g) having the following physical data, was collected by filtration and dried in vacuum.

NMR (200MHz, DMSO-d<sub>6</sub>): δ 7.19 (d, 1H), 7.69 (dd, 1H), 7.82 (d, 1H), 11.28 (broad, 1H), 11.45 (broad, 1H).

Reference example 12

4-chloro-2-chloromethylquinazoline

[0167]

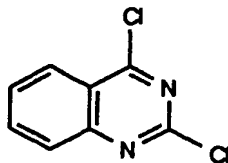


[0168] To a solution of anthranilonitrile (11.8 g) and chloroacetonitrile (7.5 g) in 1,4-dioxane (200 mL), cooled in an ice bath, was bubbled HCl gas. The reaction mixture was stirred for two and one-half hours at which time the reaction was allowed to warm to room temperature and continued to bubble HCl gas for 16 hours. After the HCl gas bubbling was ceased, nitrogen gas was bubbled through to remove any unreacted HCl gas. The mixture was concentrated at 45 °C in vacuo. The mixture was partitioned between methylene chloride (300 mL) and water (400 mL). The organic layer was separated, dried over anhydrous magnesium sulfate, and concentrated. The concentrate was dissolved in 200 mL of warm hexane, filtered and allowed to cool to room temperature. The title compound ( 9.1 g) was collected by filtration.

Reference example 13

2,4-dichloroquinazoline

[0169]



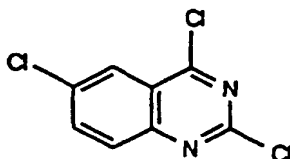
[0170] A mixture of benzoyleneurea (20.0 g), phosphorus oxychloride (100 mL) and N,N-dimethylaniline (12 mL) was refluxed for five hours. After stirring overnight at room temperature, the mixture was heated to reflux once more for an additional four hours. The cooled mixture was then poured into ice and the precipitate collected. The precipitate was purified on silica gel column with 5% methanol/chloroform as eluent. The isolated product was triturated in ether/hexane and collected to obtain the title compound (6.9 g).

[0171] The following compound was obtained by the same procedure as Reference example 13, by using 6-chloro-(1H,3H)-quinazolin-2,4-dione prepared by Reference example 11.

Reference example 13(a)

2,4,6-trichloroquinazoline

[0172]



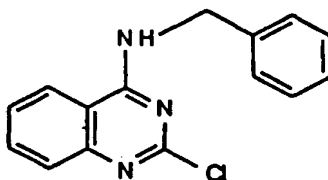
mp :125 °C.

NMR (200MHz, DMSO-d6):  $\delta$  8.09 (d, 1H), 8.21 (dd, 1H), 8.33 (d, 1H).

Reference example 14

4-phenylmethylamino-2-chloroquinazoline

[0173]



[0174] The title compound having the following physical data, was obtained by the same procedure as Example 1, by using the dichloroquinazoline prepared in Reference example 13 and phenylmethylamine (equivalent to dichloroquinazoline).

mp : 178-180 °C.

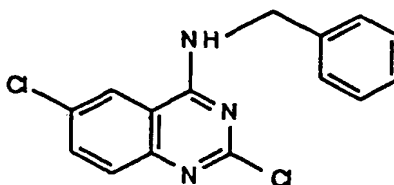
NMR (CDCl<sub>3</sub>):  $\delta$  4.86 (d, 2H), 6.05 (s, 1H), 7.32-7.51 (m, 6H), 7.62-7.85 (m, 3H).

[0175] The following compounds were obtained by the same procedure as Reference example 14, by using the corresponding 4-chloro compounds prepared in Reference example 13(a) and 12, respectively.

Reference example 14(a)

4-phenylmethylamino-2,6-dichloroquinazoline

[0176]



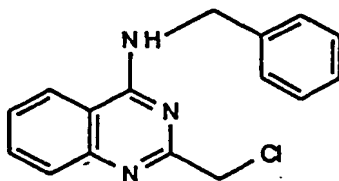
NMR (200MHz, DMSO-d6):  $\delta$  4.74 (d, 2H), 7.28-7.43 (m, 5H), 7.67 (d, 1H), 7.85 (dd, 1H), 8.50 (d, 1H), 9.36 (broad, 1H).



Reference example 14(b)

4-phenylmethylamino-2-chloromethylquinazoline

[0177]

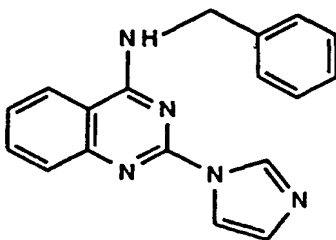


mp : 137-139 °C.

NMR (CDCl<sub>3</sub>): δ 4.68 (s, 2H), 4.90 (d, 2H), 6.00 (bs, 1H), 7.27-7.90 (m, 9H).Example 5

4-phenylmethylamino-2-(1-imidazolyl)quinazoline

[0178]



[0179] A mixture of the 2-chloro compound (0.81 g, prepared in Reference example 14), imidazole (0.81 g) and phenol (3.0 g) was heated to reflux for four and one-half hours. The mixture was then taken up in chloroform, washed twice with sodium hydroxide solution, dried over anhydrous potassium carbonate and concentrated. The concentrate was triturated in ether and collected to obtain the title compound (0.7 g) as a yellow solid having the following physical data.

mp : 212-214°C.

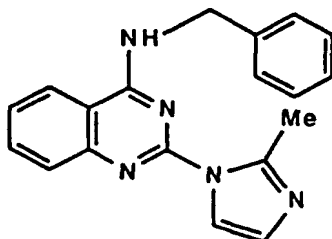
NMR (CDCl<sub>3</sub>): δ 4.86 (d, 2H), 6.05 (broad s, 1H), 7.32-7.51 (m, 6H), 7.62-7.85 (m, 3H).

[0180] The following compounds were obtained by the same procedure as Example 5, by using 4-phenylmethylamino-2-chloroquinazoline prepared in Reference example 14, 14(a) and 14(b) or corresponding quinazoline, and the proper heterocyclic compounds.

Example 5(a)

4-phenylmethylamino-2-(2-methyl-1-imidazolyl)quinazoline

[0181]

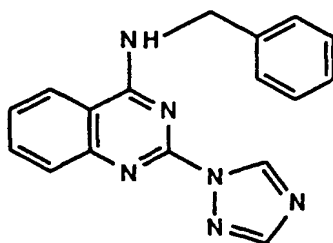


mp : 182-186 °C.

NMR (CDCl<sub>3</sub>): δ 2.89 (s, 3H), 4.92 (d, 2H), 6.30 (broad, 1H), 6.97 (s, 1H), 7.30-7.50 (m, 5H), 7.73-7.82 (m, 3H), 7.96 (s, 1H).IR (KBr): ν 3240 (w), 3060 (w), 1618 (m), 1595 (s), 1559 (s), 1439 (m), 1403 (s), 1380 (s), 1305 (s), 766 (w), 696 (w) cm<sup>-1</sup>.Example 5(b)

4-phenylmethylamino-2-(1,2,4-triazol-1-yl)quinazoline

[0182]



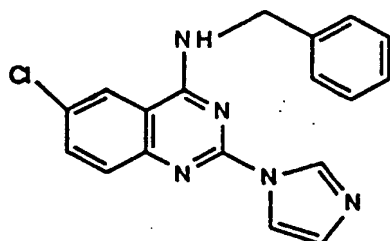
mp : 193-195 °C.

NMR (CDCl<sub>3</sub>): δ 4.73 (d, 2H), 6.02 (bs, 1H), 7.17-7.74 (m, 8H), 7.59-7.65 (m, 3H).IR (KBr): ν 3240 (w), 3125 (w), 1618 (m), 1596 (s), 1580 (s), 1547 (s), 1491 (m), 1384 (s), 1314 (s), 1207 (s), 1052 (w), 763 (m), 698 (m) cm<sup>-1</sup>.

Example 5(c)

4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline

[0183]



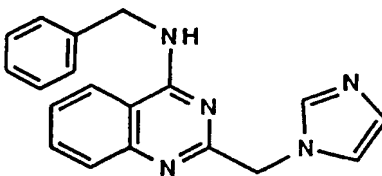
mp : 260-264 °C (dec.).

NMR (200MHz, DMSO-d6):  $\delta$  4.84 (d, 2H), 7.09 (s, 1H), 7.28-7.50 (m, 5H), 7.70 (d, 1H), 7.82 (dd, 1H), 7.93 (s, 1H), 8.52 (d, 1H), 8.56 (s, 1H), 9.40 (broad, 1H).

Example 5(d)

4-phenylmethylamino-2-((1-imidazolyl)methyl)quinazoline

[0184]



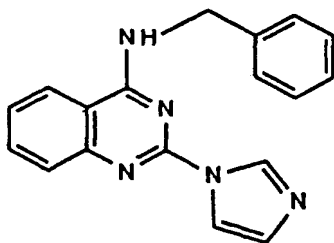
mp : 174 - 176 °C.

NMR (200MHz, DMSO-d6):  $\delta$  4.70 (d, 2H), 5.18 (s, 2H), 6.88 (s, 1H), 7.16 (s, 1H), 7.17-7.40 (m, 4H), 7.50 (m, 1H), 7.60-7.82 (m, 3H), 8.28 (d, 1H), 8.92 (m, 1H).

Example 6

4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride

[0185]



2HCl

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[0186] The title compound having the following physical data, was obtained by the same procedure as Example 2, by using the free base prepared in Example 5 and HCl/methanol solution.

mp : 248-250 °C.

NMR (200MHz, DMSO-d6):  $\delta$  4.96 (d, 2H), 7.20-7.40 (m, 3H), 7.50-7.54 (m, 2H), 7.63 (t, 1H), 7.75-7.81 (m, 1H), 7.88-7.90 (m, 2H), 8.43 (s, 1H), 8.55 (d, 1H), 9.85 (broad t, 1H), 10.03 (s, 1H).

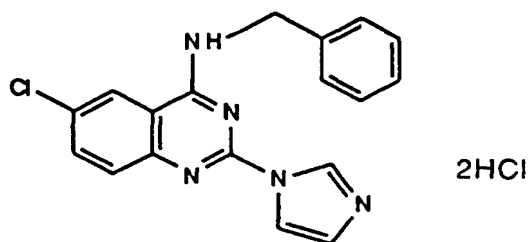
IR (KBr):  $\nu$  3055 (broad), 2655 (broad), 1634 (s), 1569 (s), 1520 (m), 1472 (m), 1395 (s), 760 (w)  $\text{cm}^{-1}$ .

[0187] By the same procedure as described in Reference example 13 and 14 and Example 5 and 6, the below compounds having the following physical data were given.

Example 6(a)

4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline dihydrochloride

[0188]



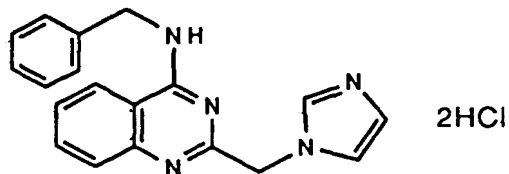
mp : 186 °C (dec.).

NMR (200MHz, DMSO-d6):  $\delta$  4.95 (m, 2H), 7.25-7.40 (m, 3H), 7.49-7.53 (m, 2H), 7.78 (d, 1H), 7.90 (t, 1H), 7.92 (dd, 1H), 8.43 (t, 1H), 8.71 (d, 1H), 9.88 (broad, 1H), 10.03 (t, 1H).

Example 6(b)

4-phenylmethylamino-2-((1-imidazolyl)methyl)quinazoline dihydrochloride

[0189]



mp : 306 °C(dec.).

NMR (200MHz, DMSO-d6):  $\delta$  4.64 (m, 2H), 5.81 (s, 2H), 7.17-7.40 (m, 5H), 7.68-8.10 (m, 5H), 8.68 (m, 1H), 9.26 (s, 1H).

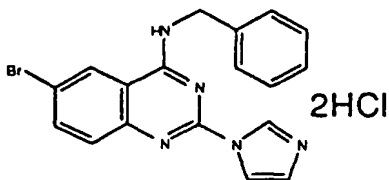
[0190] The following compound was obtained by the same procedure as described in Reference example 13, 14 and example 5 and 6, by using the corresponding (1H,3H)-quinazoline-2,4-dione or its derivative and corresponding amine.

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Example 6(c)

6-bromo-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride

[0191]



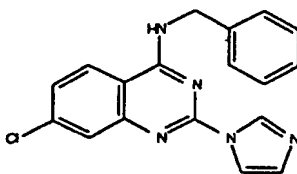
mp : 199-202 °C, (dec.)

NMR (200MHz, DMSO-d6)  $\delta$ : 4.95 (m, 2H), 7.25-7.40 (m, 3H), 7.49-7.53 (m, 2H), 7.70 (d, 1H), 7.81 (t, 1H), 8.01 (dt, 1H), 8.38 (d, 1H), 8.81 (d, 1H), 9.80 (broad, 1H), 9.88 (d, 1H).

Example 6(d)

7-chloro-4-phenylmethylamino-2-(1-imidazolyl)quinazoline

[0192]



mp : 265-268° C

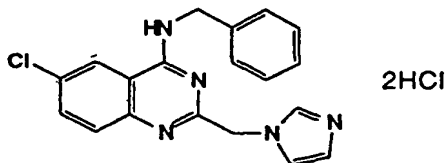
NMR (200MHz, DMSO-d6) :  $\delta$  4.85 (s, 2H), 7.08 (s, 1H), 7.21-7.40 (m, 3H), 7.42-7.58 (m, 2H), 7.71 (s, 1H), 7.91 (s, 1H), 8.35 (d, 1H), 8.54 (s, 1H).

IR (KBr):  $\nu$  3260 (w), 3135 (w), 1609 (s), 1570 (s), 1473 (s), 1451 (s), 1418 (s), 1349 (m), 1307 (m), 1037 (m), 778 (w), 698 (w)  $\text{cm}^{-1}$ .

Example 6(e)

6-chloro-4-phenylmethylamino-2-(1-imidazolymethyl)quinazoline dihydrochloride

[0193]



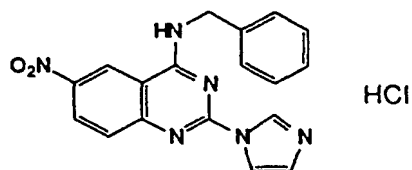
mp : 290 °C, (dec.)

NMR (200MHz, DMSO-d6)  $\delta$ : 4.66 (d, 2H), 5.72 (s, 2H), 7.18-7.42 (m, 5H), 7.72-8.05 (m, 4H), 8.76 (s, 1H), 9.27 (s, 1H).

Example 6(f)

6-nitro-4-phenylmethylamino-2-(1-imidazolyl)quinazoline hydrochloride

[0194]



mp : 190 °C, (dec.)

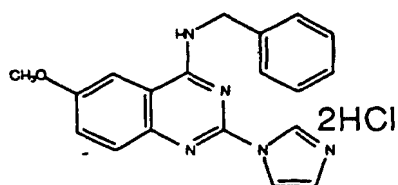
NMR (200MHz, DMSO-d6)  $\delta$ : 5.00 (m, 2H), 7.25-7.42 (m, 3H), 7.45-7.53 (m, 2H), 7.76 (broad, 1H), 7.87-7.93 (d, 1H), 8.39 (broad, 1H), 8.57-8.65 (d, 1H), 9.56 (s, 1H), 9.82 (broad, 1H), 10.28 (broad, 1H).

IR (KBr)  $\nu$ : 1335(s), 1403(s), 1438(w), 1518(w), 1601(s), 3405(broad), 3445(w)  $\text{cm}^{-1}$ .

Example 6(g)

6-methoxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride

[0195]



mp : 196 °C, (dec.)

NMR (200MHz, DMSO-d6)  $\delta$ : 3.93 (s, 3H), 4.98 (m, 2H), 7.25-7.42 (m, 3H), 7.45-7.57 (m, 2H), 7.74 (d, 1H), 7.87 (d, 1H), 7.95 (d, 1H), 8.41 (d, 1H), 9.55 (broad, 1H), 9.96 (d, 1H).

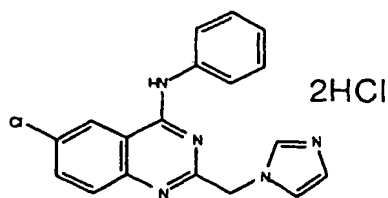
IR (KBr)  $\nu$ : 1254(m), 1395(s), 1506(m), 1558(s), 1601(s), 3065(w), 3245(w), and 3395(w)  $\text{cm}^{-1}$ .

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Example 6(h)

6-chloro-4-phenylamino-2-(1-imidazolylmethyl)quinazoline dihydrochloride

[0196]



mp : 280 °C, (dec.)

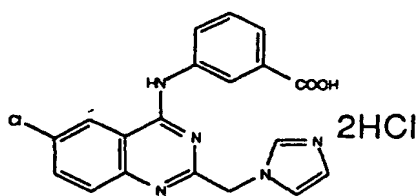
NMR (200MHz, DMSO-d6)  $\delta$ : 5.72 (s, 2H), 7.12-8.03 (m, 9H), 8.99 (m, 1H), 9.26 (s, 1 H), 10.65 (bs, 1H).

IR (KBr)  $\nu$ : 3100 (m), 2830 (m), 2565 (m), 1635 (m), 1608 (m), 1578 (sd), 1492 (ms), 1151 (m)  $\text{cm}^{-1}$ .

Example 6(i)

6-chloro-4-(3-carboxyphenyl)amino-2-(1-imidazolylmethyl)quinazoline dihydrochloride

[0197]



mp : 285 °C, (dec.)

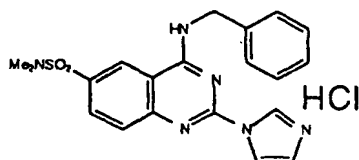
NMR (200MHz, DMSO-d6)  $\delta$ : 5.69 (s, 2H), 7.49 (t, 1H), 7.70-8.02 (m, 6H), 8.26 (m, 1H), 8.90 (m, 1H), 9.26 (s, 1H), 10.50 (bs, 1H).

IR (KBr)  $\nu$ : 3326 (m), 3065 (m), 2835 (m), 1698 (m), 1631 (m), 1602 (m), 1561 (s), 1486 (m), 1444 (m), 1400 (m), 1376 (mw)  $\text{cm}^{-1}$ .

Example 6(j)

6-dimethylaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline hydrochloride

[0198]



mp : 264-266°C.

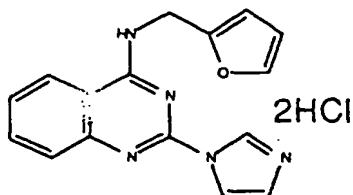
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NMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$ : 2.69(s, 6H), 5.00(d, 2H), 7.25-7.45(m, 3H), 7.46-7.54(m, 2H), 7.78(m, 1H), 7.93(dd, 1H), 8.13(d, 1H), 8.40(m, 1H), 8.95(m, 1H), 9.84(m, 1H), 10.13(br, 1H).  
IR (KBr):  $\nu$  3400(m), 3320(m), 2960(w), 1597(s), 1556(m), 1520(m), 1445(m), 1398(s), 1341 (s), 1164(s), 728(s), 579 (s) cm<sup>-1</sup>.

Example 6(k)

4-(2-furylmethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride

[0199]



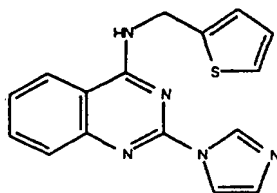
mp : 230 °C, (dec.)

NMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$ : 4.99 (d, 2H), 6.48 (m, 2H), 7.57-7.97 (m, 5H), 8.49 (m, 2H), 9.64 (t, 1H), 10.08 (s, H).

Example 6(l)

4-(2-thienylmethyl)amino-2-(1-imidazolyl)quinazoline

[0200]



mp : 234-235° C

NMR (200MHz, DMSO-d<sub>6</sub>):  $\delta$  5.03 (d, 2H), 7.00 (m, 1H), 7.13 (s, 1H), 7.18 (d, 1H), 7.37 (d, 1H), 7.52 (t, 1H), 7.78 (m, 2H), 8.02 (s, 1H), 8.28 (d, 1H), 8.67 (s, 1H), 9.40 (t, 1H).

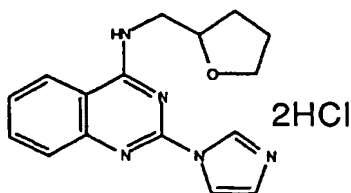
IR (KBr):  $\nu$  3255 (w, broad), 1617 (w), 1668 (s), 1470 (s), 1402 (s), 1321 (m) cm<sup>-1</sup>.



Example 6(m)

4-(2-tetrahydrofuranylmethyl)amino-2-(1-imidazolyl)quinazoline

[0201]



mp : 98-150°C

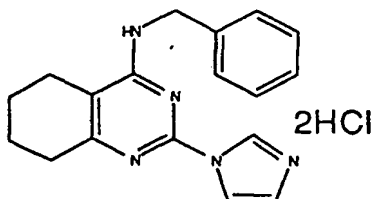
NMR (200MHz, DMSO-d<sub>6</sub>) δ: 1.62-2.13 (m, 4H), 3.62-3.90 (m, 4H), 4.12-4.31 (m, 2H), 7.54-7.97 (m, 4H), 8.44 (s, 1H), 9.32 (t, 1H), 10.02 (s, 1H).

IR (KBr) ν: 3500-2700 (s, broad), 1635 (m), 1576 (m), 1396 (m), 1063 (w), 765 (w) cm<sup>-1</sup>.

Example 6(o)

4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydro-quinazoline dihydrochloride

[0202]



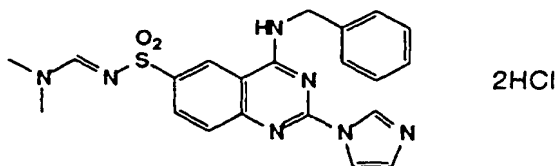
mp : 195 °C, (dec.)

NMR (200MHz, DMSO-d<sub>6</sub>) δ: 1.79 (m, 4H), 2.45 (m, 2H), 2.66 (m, 2H), 4.74 (d, 2H), 7.17-7.48 (m, 5H), 7.83 (cs, 1H), 8.13 (t, 1H), 8.24 (cs, 1H), 9.84 (cs, 1H).

Example 6(p)

6-dimethylaminomethylideneaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride

[0203]



mp : 225 °C

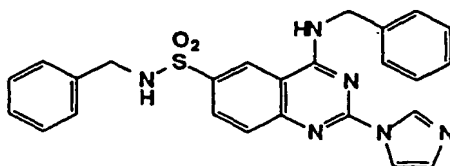
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NMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$ : 2.93 (s, 3H), 3.18 (s, 3H), 4.97 (d, 2H), 7.25-7.40 (m, 3H), 7.49-7.53 (m, 2H), 7.79 (s, 1H), 7.84 (d, 1H), 8.15 (dt, 1H), 8.30 (s, 1H), 8.39 (s, 1H), 9.00 (s, 1H), 9.86 (s, 1H), 10.10 (t, 1H).

Example 6(q)

6-(phenylmethylaminosulfonyl)-4-phenylmethylamino-2-(1-imidazolyl)quinazoline

[0204]



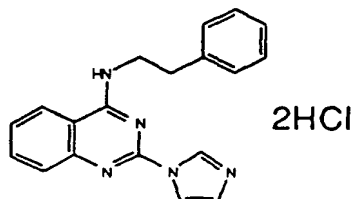
mp : 207-8 °C

NMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$ : 4.09 (d, 2H), 4.89 (m, 2H), 7.11 (s, 1H), 7.16-7.52 (m, 10H), 7.79 (d, 1H), 7.96 (d, 1H), 8.07 (dd, 1H), 8.28 (t, 1H), 8.60 (s, 1H), 8.83 (m, 1 H), 9.80 (broad t, 1H).

Example 6(r)

4-(2-phenylethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride

[0205]



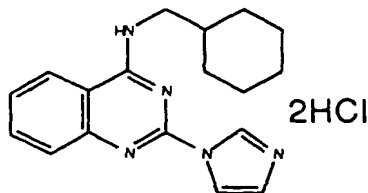
mp : 70-100 °C

NMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$ : 3.05 (t, 2H), 3.95 (q, 2H), 7.12-7.38 (m, 6H), 7.57 (t, 1H), 7.73 (m, 2H), 7.89 (m, 3H), 8.41 (m, 2H), 9.38 (t, 1H), 9.96 (s, 1H).

Example 6(s)

4-cyclohexylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride

[0206]



mp : 140-150 °C

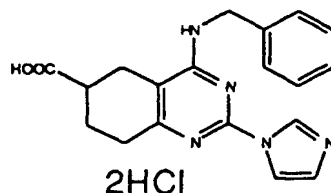
NMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$ : 0.98-1.32 (m, 5H), 1.53-1.90 (m, 6H), 3.58 (t, 2H), 7.59 (t, 1H), 7.77 (m, 1H), 7.89 (t,

2H), 8.41 (s, 1H), 8.56 (d, 1H), 9.28 (t, 1H), 9.97 (s, 1H).

Example 6(t)

6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline dihydrochloride

[0207]



mp : 105 °C (dec.)

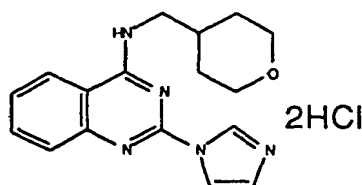
NMR (200MHz, DMSO-d<sub>6</sub>) δ: 1.82 (m, 1H), 2.10 (m, 1H), 2.71 (m, 5H), 4.74 (d, 2H), 7.18-7.47 (m, 5H), 7.82 (s, 1H), 8.24 (s, 1H), 8.25 (m, 1H), 9.84 (s, 1H).

IR (KBr) v: 3140 (bm), 2935 (bm), 1718 (mw), 1654 (m), 1617 (ms), 1522 (mw), 1394 (m) cm<sup>-1</sup>.

Example 6(v)

4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride

[0208]



mp : 160-195 °C

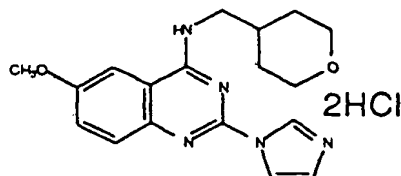
NMR (200MHz, DMSO-d<sub>6</sub>) δ: 10.0 (m, 1H), 9.29 (m, 1H), 8.53 (d, 1H), 8.45 (m, 1H), 7.82-7.95 (d, 2H), 7.75 (d, 1H), 7.60 (t, 1H), 3.86 (m, 2H), 3.64 (m, 2H), 3.28 (t, 2H), 2.02 (m, 1H), 1.60-1.75 (m, 2H), 1.21-1.48 (m, 2H).

IR (KBr) v: 1635, 1604, 1562, 1524, 1471, 1443, 1393, 1091, 762 cm<sup>-1</sup>.

Example 6(w)

6-methoxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride

[0209]



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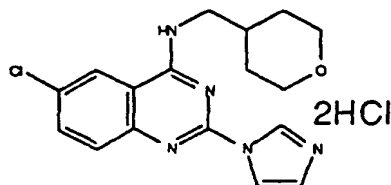
mp : 170-190 °C

NMR (200MHz, DMSO-d6)  $\delta$ : 9.96 (s, 1H), 9.15 (m, 1H), 9.42 (s, 1H), 7.98 (s, 1H), 7.89 (s, 1H), 7.71 (d, 1H), 7.52 (dd, 1H), 3.94 (s, 3H), 3.80-3.95 (m, 2H), 3.62 (m, 2H), 3.29 (t, 2H), 2.02 (m, 1H), 1.60-1.75 (m, 2H), 1.20-1.49 (m, 2H). IR (KBr)  $\nu$ : 1637, 1605, 1569, 1524, 1473, 1440, 1391, 1251, 1091, 1020  $\text{cm}^{-1}$ .

Example 6(x)

6-chloro-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride

[0210]



mp : 155-185 °C

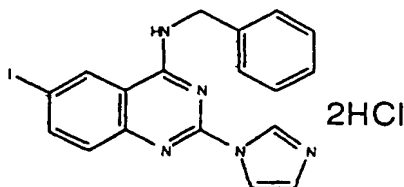
NMR (200MHz, DMSO-d6)  $\delta$ : 9.89 (s, 1H), 9.25 (m, 1H), 8.66 (m, 1H), 8.41 (m, 1H), 7.72-7.96 (m, 3H), 3.81-3.95 (m, 2H), 3.56-3.70 (m, 2H), 3.28 (t, 2H), 2.02 (m, 1H), 1.63-1.79 (m, 2H), 1.20-1.46 (m, 2H).

IR (KBr)  $\nu$ : 1604, 1577, 1524, 1497, 1446, 1396, 1349, 1089  $\text{cm}^{-1}$ .

Example 6(y)

6-iodo-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride

[0211]



mp : 183 °C, (dec.)

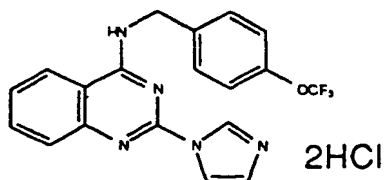
NMR (200MHz, DMSO-d6)  $\delta$ : 4.95 (m, 2H), 7.25-7.40 (m, 3H), 7.45-7.60 (m, 3H), 7.88 (t, 1H), 8.16 (dt, 1H), 8.43 (t, 1H), 8.93 (s, 1H), 9.78 (t, 1H), 10.01 (d, 1H).

IR (KBr)  $\nu$ : 3060, 2685, 1634, 1600, 1541, 1406, 1390  $\text{cm}^{-1}$ .

example 6(z)

4-(4-trifluoromethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride

[0212]



mp : 140-145 °C

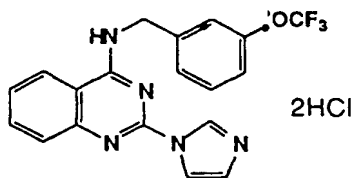
NMR (200MHz, DMSO-d6)  $\delta$ : 5.01 (m, 2H), 7.30-7.40 (m, 2H), 7.60-7.88 (m, 6H), 8.42-8.55 (m, 2H), 9.78 (bm, 1H), 10.35 (s, 1H).

IR (KBr)  $\nu$ : 3070, 1634, 1604, 1560, 1525, 1394, 1263, 1224, 1164  $\text{cm}^{-1}$ .

Example 6(aa)

4-(3-trifluoromethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride

[0213]



(2HCl salt)

mp : 170-180°C

NMR (200MHz, DMSO-d6):  $\delta$  5.01 (d, 2H), 7.25(d, 1H), 7.42-7.71(m, 3H), 7.81 (s, 1H), 7.88(m, 2H), 8.44(s, 1H), 8.54 (d, 1H), 9.95(t, 1H), 10.06(s, 1H). IR(KBr):  $\nu$  3430(w), 3020(w), 2960(w), 1653(s), 1603(s), 1542(m), 1396(s), 1270(s), 1216(m)  $\text{cm}^{-1}$

Example 6(bb)

6-methoxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride

[0214]



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(2HCl salt)

mp : 167.5-170°C

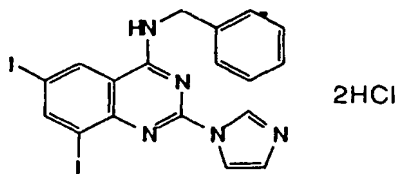
NMR (200MHz, DMSO-d6):  $\delta$  3.51(s, 4H), 3.75-3.78(m, 2H), 3.85-3.90(m, 2H), 3.93(s, 3H), 7.49(dd, 1H), 7.70(d, 1H), 7.84(t, 1H), 7.98(m, 1H), 8.39(m, 1H), 9.19(br, 1H), 9.90(t, 1H).

IR(KBr):  $\nu$  3270(s), 2940(m), 1610(s), 1557(m), 1513(s), 1396(s), 1247(m), 1115(m), 1029(w)  $\text{cm}^{-1}$

Example 6(ee)

4-phenylmethylamino-6,8-diiodo-2-(1-imidazolyl)quinazoline dihydrochloride

[0215]



(2HCl salt)

mp : 303-304°C (dec.)

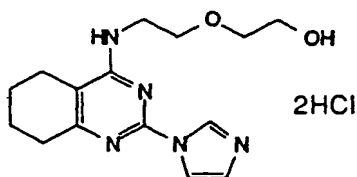
NMR (200MHz, DMSO-d6):  $\delta$  4.94(d, 2H), 7.33(dd, 3H), 7.49(dd, 2H), 7.74(t, 1H), 8.24(t, 1H), 8.67(t, 1H), 8.88(d, 1H), 9.66(s, 1H), 9.77(br, 1H).

IR(KBr):  $\nu$  3410-2365(br, m), 1599(s), 1437(m), 1387(s), 1350(m), 1314(m), 1273(w), 1061(w), 1020(w), 793(w), 748(w), 701(w), 620(w)  $\text{cm}^{-1}$

Example 6(ii)

4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline dihydrochloride

[0216]



(2HCl salt)

mp : 125-128°C

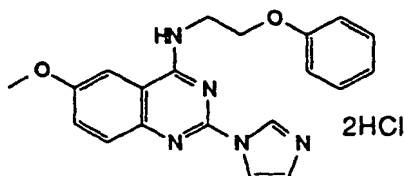
NMR (200MHz, DMSO-d6):  $\delta$  1.80(4H), 2.40(2H), 3.65(br, 8H), 7.45(br, 1H), 7.85(d, 1H), 8.30(d, 1H), 9.85(d, 1H).

IR(KBr):  $\nu$  3380(s), 3120(s), 2945(m), 2755-2460(m), 1615(s), 1540(s), 1457(m), 1428(m), 1390(s), 1350(m), 1319(w), 1103(m), 1070(m), 829(w), 624(w)  $\text{cm}^{-1}$

Example 6(ii)

4-(2-phenoxyethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline and its dihydrochloride

[0217]



(free base)

mp : 213-214°C

NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.89 (s, 3H), 4.04(d, 2H), 4.31 (t, 2H), 6.93-7.01 (3H), 7.08(d, 1H), 7.28(td, 2H), 7.45 (dd, 1H), 7.64(d, 1H), 7.78(d, 1H), 7.93(t, 1H), 8.57(s, 1H), 9.85(br, 1H).IR(KBr): ν 1599(s), 1555(s), 1491 (s), 1409(s), 1382(w), 1310(m), 1242(s), 1051(s), 752(w) cm<sup>-1</sup>

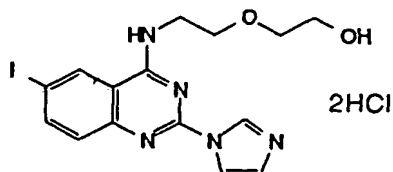
(2HCl salt)

mp : 184-186°C

NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.94(s, 3H), 4.12(d, 2H), 4.33(t, 2H), 6.90-7.01 (3H), 7.29(t, 2H), 7.53(dd, 1H), 7.88 (t, 1H), 7.96(d, 1H), 8.40(t, 1H), 9.31 (br, 1H), 9.93(d, 1H).IR(KBr): ν 3050(m), 2840-2335(m), 1637(s), 1598(s), 1497(m), 1472(m), 1380(s), 1258(s), 1122(w), 1077(w), 1029 (m), 775(m), 747(m) cm<sup>-1</sup>Example 6(kk)

4-(2-(2-hydroxyethoxy)ethyl)amino-6-iodo-2-(1-imidazolyl)quinazoline and its dihydrochloride

[0218]



(free base)

NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.50(s, 4H), 3.75(dd, 2H), 3.78(d, 2H), 4.59(br, 1H), 7.10(d, 1H), 7.47(dd, 1H), 7.95 (d, 1H), 8.05(d, 1H), 8.52(d, 1H), 8.75(s, 1H), 8.57(br, 1H).

(2HCl salt)

mp : 132-135°C

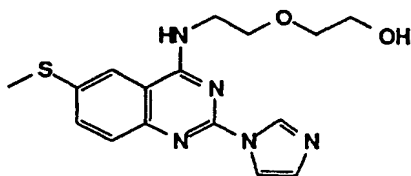
NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.50(s, 4H), 3.75(d, 2H), 3.86(d, 2H), 7.53(d, 1H), 7.83(s, 1H), 8.15(dd, 1H), 8.40 (s, 1H), 8.89(d, 1H), 9.22(br, 1H), 9.90(s, 1H).IR(KBr): ν 3230-2720(br, m), 1607(s), 1555(m), 1526(m), 1492(m), 1445(m), 1394(s), 1348(m), 1118(m), 1063(m), 1027(m), 859(m), 622 cm<sup>-1</sup>

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Example 6(mm)

4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline

[0219]



(free base)

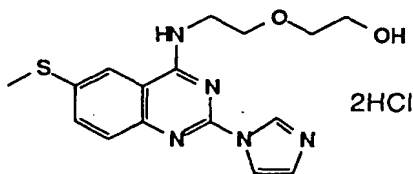
mp : 169-172 °C

NMR (200MHz, DMSO-d6):  $\delta$  2.61 (s, 3H), 3.51(s, 4H), 3.76 (m, 4H), 4.60(m, 1H), 7.10(s, 1H), 7.57-7.76(m, 2H), 7.95 (s, 1H), 8.09(s, 1H), 8.59(s, 1H), 8.82(m, 1H).

Example 6(nn)

4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline dihydrochloride

[0220]



(2HCl salt)

mp : 180-182 °C.

NMR (200MHz, DMSO-d6):  $\delta$  2.65(s, 3H), 3.51 (s, 4H), 3.75(m, 2H), 3.90(m, 2H), 7.64-7.82(m, 2H), 7.87(m, 1H), 8.26 (m, 1H), 8.42(1 H), 9.34(t, 1H), 9.98(m, 1H).

Example 6(rr)

4-[2-(2-hydroxyethoxy)ethyl]amino-6-methoxycarbonyl-2-(1-imidazolyl)-quinazoline

[0221]



mp : 233-235°C.

NMR (200MHz, DMSO-d6):  $\delta$  3.50(m, 4H), 3.70-3.90(m, 4H), 3.93(s, 3H), 4.60(m, 1H), 7.12(s, 1H), 7.75(d, 1H), 7.99 (s, 1H), 8.25(dd, 1H), 8.63(s, 1H), 9.03(m, 1H), 9.28(m, 1H).



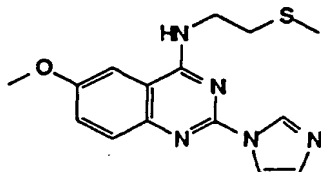
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IR (KBr) :  $\nu$  3245(mw), 2950(w), 1730(ms), 1626(w), 1603(s), 1558(m), 1474(m), 1437(m), 1406(m), 1309(m), 1281(w), 1229(w), 1125(w), 1102(w), 1051 (w)  $\text{cm}^{-1}$ .

Example 6(ss)

4-(2-methylthioethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline

[0222]



mp : 168-178°C.

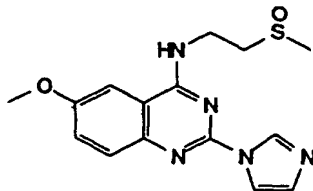
NMR (200MHz, DMSO-d<sub>6</sub>):  $\delta$  2.17(s, 3H), 2.89(t, 2H), 3.90(m, 2H), 3.93(s, 3H), 7.55(dd, 1H), 7.69(d, 1H), 7.87(s, 1H), 7.97(s, 1H), 8.40(s, 1H), 9.34(t, 1H), 9.93(s, 1H).

IR (KBr) :  $\nu$  3410, 3095, 2675, 1635, 1609, 1587, 1400, 1264, 1018  $\text{cm}^{-1}$ .

Example 6(tt)

4-(2-methylsulfinylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline

[0223]



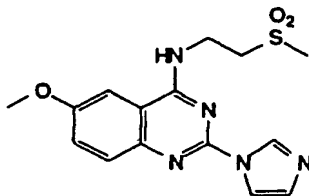
mp : 238-242°C.

NMR (200MHz, DMSO-d<sub>6</sub>):  $\delta$  2.63(s, 3H), 3.10-3.70(m, 4H), 3.92(s, 3H), 7.53(dd, 1H), 7.72(d, 1H), 7.88(d, 2H), 8.48(s, 1H), 9.43(m, 1H), 10.01 (s, 1H). IR (KBr) :  $\nu$  3435, 3005, 2710, 1625, 1560, 1398, 1248, 1020, 825  $\text{cm}^{-1}$ .

Example 6(uu)

4-(2-methylsulfonylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline

[0224]



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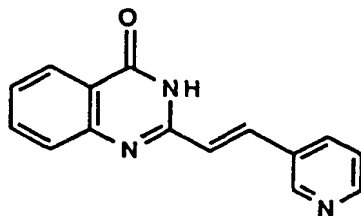
mp : 245-252°C.

NMR (200MHz, DMSO-d6):  $\delta$  3.09(s, 3H), 3.61 (t, 2H), 3.92(s, 3H), 4.09(m, 2H), 7.54(dd, 1H), 7.76(d, 1H), 7.88(s, 2H), 8.45(s, 1H), 9.38(br, 1H), 9.89(s, 1H).

Reference example 15

2-(2-(3-pyridyl)vinyl)quinazolin-4-one

[0225]

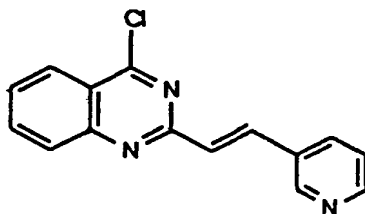


[0226] A mixture of 2-methylquinazolin-4-one (6.1 g) and 3-pyridinecarbaldehyde (4.1 g) in acetic acid (80 mL) was heated to reflux for 20 hours. After cooling to room temperature, the precipitate was collected by filtration, washed with methanol and dried to obtain the title compound as an acetic acid salt (10.5 g).

Reference example 16

4-chloro-2-(2-(3-pyridyl)vinyl)quinazoline

[0227]

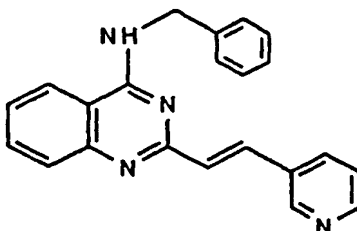


[0228] A suspension of the quinazolinone compound (2.9 g, prepared in Reference example 15) in thionyl chloride (25 mL) and a few drops of dimethylformamide was heated at reflux for three hours. The mixture was then concentrated, the concentrate poured into 150 mL portions of chloroform, dried over potassium carbonate and concentrated to obtain the title compound (1.1 g) as a red oil.

Example 7

4-phenylmethylamino-2-(2-(3-pyridyl)vinyl)quinazoline

[0229]



[0230] The title compound having the following physical data, was obtained by the same procedure as Example 1, by using the 4-chloro compound prepared in Reference example 16 and phenylmethylamine.

The product was purified by column chromatography.

mp : 178-179 °C.

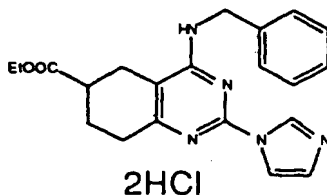
NMR (CDCl<sub>3</sub>): δ 4.96 (d, 2H), 6.11 (broad, 1H), 7.30-7.55 (m, 8H), 7.70-7.81 (m, 2H), 7.99 (d, 1H), 8.34 (s, 1H), 8.36-8.45 (m, 1H), 8.55-8.58 (dd, 1H), 8.90-8.91 (d, 1H).

IR (KBr): ν 3300 (m), 1577 (s), 1528 (s), 1434 (m), 1378 (s), 763 (m), 699 (m) cm<sup>-1</sup>

Example 8

6-ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline and its salt

[0231]



[0232] To 349 mg (1.0 mmol) of a compound prepared in example 6(t) dissolved in 20 mL of tetrahydrofuran was added 0.4 mL of thionyl chloride. Initially, a white precipitate formed, but gradually all dissolved. After stirring for 15 minutes, 20 mL of ethanol was added. After stirring an additional 15 minutes, the mixture was concentrated, the concentrate triturated in ether and collected. The solid was found to be very hygroscopic, was taken up in chloroform, treated with potassium carbonate solution, separated, dried over anhydrous magnesium sulfate and concentrated. Obtained 278 mg (0.7 mmol, 73% yield) of the desired product as a white solid (free base).

(free base)

mp : 196-198°C

NMR (DMSO-d<sub>6</sub>): δ 1.30 (t, 3H), 1.90 (m, 1H), 2.28 (m, 1H), 2.60 (m, 2H), 2.82 (m, 3H), 4.23 (q, 2H), 4.77 (d, 2H), 5.12 (m, 1H), 7.10 (s, 1H), 7.37 (m, 5H), 7.83 (s, 1H), 8.54 (s, 1H).

IR (KBr): 3245 (w), 1725 (ms), 1605 (s), 1532 (w), 1473 (m), 1426 (m), 1333 (w) cm<sup>-1</sup>.

[0233] To a suspension of 240 mg (0.64 mmol) of the compound prepared above in 5 mL of ethanol was added 2 mL of ~10% HCl in methanol. All the material gradually dissolved. After ten minutes, the mixture was concentrated in vacuo, triturated in ether and filtered to obtain 229 mg (0.51 mmol) of the desired product.

(2HCl salt)

mp : 158-161 °C

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NMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$ : 1.22 (t, 3H), 1.87(m, 1H), 2.14 (m, 1H), 2.55-3.00 (m, 5H), 7.79 (s, 1H), 8.23 (s, 1H), 9.77 (s, 1H).

IR (KBr)  $\nu$ : 3225, 1718, 1642, 1612, 1518, 1393 cm<sup>-1</sup>.

Example 8(a)

6-ethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline dihydrochloride

[0234]



[0235] By the same procedure as described in example 8, by using ethylamine instead of ethanol, the title compound having the following physical data was given.

mp : 147 °C, (dec.)

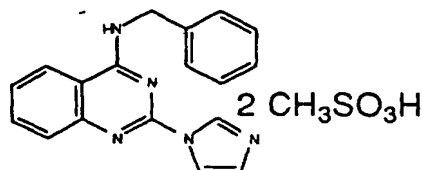
NMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$ : 1.04 (q, 3H), 1.65-2.06 (m, 2H), 2.50-2.80 (m, 5H), 3.10 (m, 2H), 4.72 (m, 2H), 7.18-7.48 (m, 5H), 7.81 (s, 1H), 8.05 (t, 1H), 8.18 (M, 1H), 8.24 (m, 1H), 9.82 (s, 1H).

IR (KBr)  $\nu$ : 3265-2580, 2365, 1653, 1613, 1576, 1540, 1449, 1390, 1352, 1144, 1060, 750, 701, 624 cm<sup>-1</sup>.

Example 9

4-phenylmethylamino-2-(1-imidazolyl)quinazoline dimethanesulfonate

[0236]



[0237] By the same procedure as described in Reference example 13 and 14 and example 5 and 6, by using methanesulfonic acid instead of hydrochloric acid, the title compound and the following compounds having the following physical data were given.

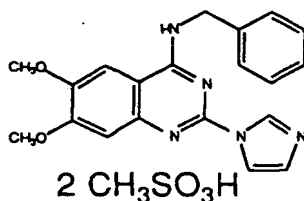
mp : 140-143 °C

NMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$ : 2.38 (s, 6H), 4.95 (m, 2H), 7.20-8.00 (m, 9H), 8.40-8.53 (m, 2H), 9.64 (t, 1H), 10.00 (s, 1H).

Example 9(a)

6,7-dimethoxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dimethanesulfonate

[0238]



mp : 205 °C, (dec.)

NMR (200MHz, DMSO-d<sub>6</sub>) δ: 2.36 (s, 6H), 3.92 (s, 3H), 3.95 (s, 3H), 4.95 (m, 2H), 7.18 (d, 1H), 7.21-7.53 (m, 5H), 7.82 (s, 1H), 7.87 (m, 1H), 8.39 (m, 1H), 9.21 (t, 1H), 9.94 (m, 1H).

Example 9(b)

4-(3,4-dimethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline 1.5 methanesulfonate

[0239]



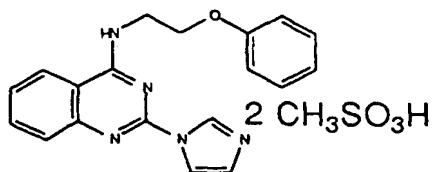
mp : 163-173 °C.

NMR (200MHz, DMSO-d<sub>6</sub>) δ: 2.34 (s, 4H), 3.73 (d, 6H), 4.88 (d, 2H), 6.02 (d, 1H), 7.03 (d, 1H), 7.16 (s, 1H), 7.62 (t, 1H), 7.78 (d, 1H), 7.89 (m, 2H), 8.45 (d, 1H), 8.48 (s, 1H), 9.55 (t, 1H), 10.02 (s, 1H).

Example 9(c)

4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline dimethanesulfonate

[0240]



mp : 144-161 °C

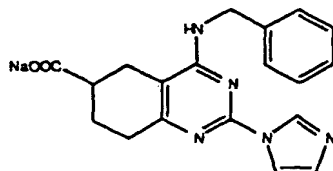
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NMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$ : 2.39 (s, 6H), 4.12 (q, 2H), 4.34 (t, 2H), 6.97 (m, 3H), 7.28 (t, 2H), 7.63 (m, 1H), 7.80 (s, 1H), 7.91 (m, 2H), 8.45 (m, 2H), 9.30 (m, 2H), 9.97 (s, 1H).  
IR (KBr)  $\nu$ : 3700-2800 (broad), 1636 (s), 1211 (s) cm<sup>-1</sup>.

## Example 10

6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline sodium salt

[0241]



[0242] A solution of 200 mg (0.57 mmol) of a compound prepared in example 6(t) dissolved in 25 mL of tetrahydrofuran was filtered to remove dark insoluble material present. To the filtrate was added 0.25 mL (0.62 mmol) of 2.5 N sodium hydroxide solution. Some precipitate formed. The mixture was concentrated and pumped in vacuum. The concentrate was triturated in tetrahydrofuran and ether and filtered. The solid was washed with ether and filtered to obtain 190 mg (0.51 mmol) of the desired product as a white solid. mp : 240 °C, (dec.)

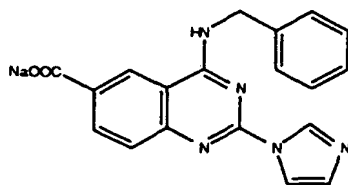
NMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$ : 1.50-1.82 (m, 2H), 1.88-2.35 (m, 2H), 2.59 (m, 3H), 4.62 (s, 2H), 6.98 (s, 1H), 7.12-7.48 (m, 5H), 7.73 (s, 1H), 7.86 (m, 1H), 8.33 (s, 1H).

[0243] By the same procedure as described in example 10, the compound having the following physical data was given.

## Example 10(a)

6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline sodium salt

[0244]



mp : >280 °C

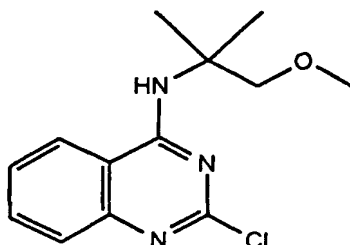
NMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$ : 4.48 (d, 2H), 6.99 (s, 1H), 7.25 (m, 1H), 7.33 (m, 4H), 7.40 (d, 1 H), 7.78 (s, 1 H), 7.97 (dd, 1H), 8.46 (s, 1 H), 8.57 (d, 1H), 9.11 (br, 1H).

IR (KBr)  $\nu$ : 3500-3100 (br), 1620, 1559, 1472, 1399, 1307, 1224, 1056, 699 cm<sup>-1</sup>.

## Reference example 17

4-(1,1-dimethyl-2-methoxyethyl)amino-2-chloroquinazoline

[0245]



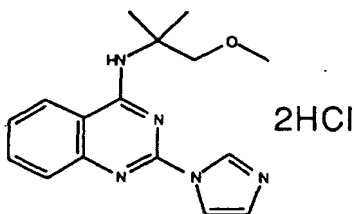
[0246] A mixture of 2,4-dichloroquinazoline (995 mg, 5 mmol), triethylamine (0.7 ml, 5 mmol) and 1,1-dimethyl-2-methoxyethylamine (30 mL, 0.5 M methanol sol., 15 mmol) was stood at room temperature for 1 week. The reaction mixture was concentrated and partitioned between ethyl acetate and water. Organic layer was washed with water and brine, dried over  $\text{MgSO}_4$  and concentrated. The residue was purified on 50 g of silica gel column eluting with 50% ethyl acetate in hexane to obtain the title compound (176 mg) as a white solid.

NMR ( $\text{CDCl}_3$ ):  $\delta$  1.60 (s, 6H), 3.46 (s, 3H), 3.56 (s, 2H), 7.38-7.80 (m, 4H).

## Reference example 17(a)

4-(1,1-dimethyl-2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride

[0247]



[0248] A mixture of the compound prepared in Reference example 17 (165 mg, 0.62 mmol), imidazole (169 mg, 2.48 mmol) and phenol (0.7 g) was heated at 150 °C for 40 min. After cooling, the reaction mixture was diluted with ethyl acetate, and washed with 1N KOH and brine, and dried over  $\text{MgSO}_4$ . The filtrate was concentrated to leave a viscous oil, which was purified on 8 g of silica gel column eluting with 50% ethyl acetate in hexane to obtain the title compound (165 mg, 90% yield) as a colorless amorphous.

(free base)

NMR ( $\text{CDCl}_3$ ):  $\delta$  1.65 (s, 6H), 3.48 (s, 3H), 3.58 (s, 2H), 6.32 (broad, 1H), 7.17 (s, 1 H), 7.40 (m, 1 H), 7.62-7.81 (m, 3H), 7.97 (s, 1H), 8.67 (s, 1H).

[0249] To a solution of the compound above (160 mg, 0.54 mmol) in methanol (2mL) was added excess HCl-methanol solution (2mL). After stirring for 20 min at room temperature, the reaction mixture was concentrated. Excess HCl was evaporated with methanol (x3) to leave a white solid Trituration with ether gave HCl salt (185 mg) as a white powder. (HCl salt)

mp : 223-225 °C

NMR (200MHz,  $\text{DMSO-d}_6$ )  $\delta$ : 9.80 (s, 1H), 8.59 (m, 1H), 8.34 (m, 1H), 7.84-7.96 (m, 3H), 7.78 (m, 1H), 7.60 (m, 1H), 3.78 (s, 2H), 3.29 (s, 3H), 1.57 (s, 6H).

IR (KBr)  $\nu$ : 1633, 1610, 1562, 1520, 1474, 1397, 1108, 754  $\text{cm}^{-1}$ .

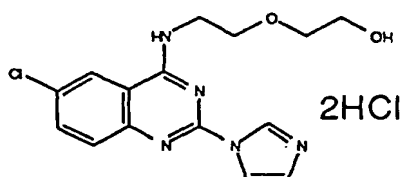
[0250] By the same procedure as described in Reference example 17 and Reference example 17(a), by using cor-

responding amine, the compound having the following physical data was given.

Example 11(e)

6-chloro-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride

[0251]



mp : 184-186 °C

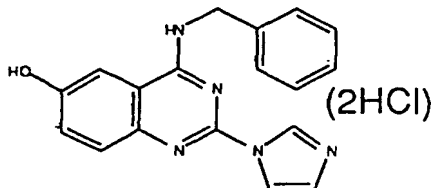
NMR (200MHz, DMSO-d<sub>6</sub>) δ: 3.51 (s, 4H), 3.75-3.77 (m, 2H), 3.85-3.90 (m, 2H), 7.76 (d, 1H), 7.84 (m, 1H), 7.91 (dd, 1H), 8.40 (t, 1H), 8.67 (m, 1H), 9.30 (bt, 1H), 9.92 (m, 1H).

IR (KBr) v: 3320, 3175-2825, 1602, 1574, 1497, 1439, 1398, 1343, 1118 cm<sup>-1</sup>.

Example 13

6-hydroxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline and its salt

[0252]



[0253] To 66 mg (0.2 mmol) of the compound prepared in Example 6(g) in 1 mL of acetic acid was added 0.8 mL (7 mmol) of 48% HBr in water. The mixture was heated below reflux for 23 hours then heated to full reflux for four hours. After cooling to room temperature, 15 mL of water was added to the solution and the precipitate was filtered and dried under vacuum. The material was purified on a preparative silica gel plate with 10% methanol in chloroform. Obtained 13 mg (41 μmol) of the desired product as a solid.

(free base)

mp : 230 °C, (dec.)

NMR (200MHz, CD<sub>3</sub>OD) δ: 4.86 (s, 2H), 7.05 (s, 1H), 7.15-7.38 (m, 4H), 7.40-7.50 (m, 3H), 7.58-7.66 (m, 1H), 7.92 (s, 1H), 8.52 (s, 1H).

IR (KBr) v: 3370, 3030, 2365, 1749, 1710, 1653, 1596, 1559, 1523, 1488, 1465, 1407, 1376, 1291, 1244, 1162, 1098, 1060, 911, 831 cm<sup>-1</sup>.

[0254] By the same procedure as described in Example 12, the hydrochloride having the following physical data was given.

(2HCl salt)

mp : 155 °C, (dec.)

NMR (200MHz, DMSO-d<sub>6</sub>) δ: 4.92 (m, 2H), 7.22-7.77 (m, 8H), 7.86 (s, 1H), 8.38 (s, 1H), 9.36 (m, 1H), 9.94 (s, 1H).

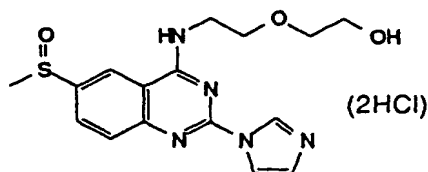
IR (KBr) v: 3395-2640, 2365, 1734, 1628, 1607, 1567, 1542, 1473, 1361, 1353, 1289, 1260, 1201, 1107, 1015, 835, 753, 702 cm<sup>-1</sup>.



Example 14

4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylsulfinyl-2-(1-imidazolyl)-quinazoline and its dihydrochloride

[0255]



[0256] To 1.38 g of the compound prepared in example 6(mm) dissolved in 10 mL of acetic acid was added 4 mL of 30% hydrogen peroxide. The reaction was monitored by TLC. After stirring for 1/2 hour, the mixture was poured into 15 g of 50% w/w sodium hydroxide and ice. The resulting mixture was extracted four times with chloroform, dried over anhydrous magnesium sulfate and concentrated. The concentrate was triturated in ether and collected to obtain 1.26 g of the desired product as a white solid.

[0257] To 400 mg of the compound prepared above in 10 ml of methanol was added 1 mL of 10% HCl in methanol. After ten minutes, the mixture was concentrated, triturated in ether and the solid collected. Obtained 441 mg of the desired product as a dihydrochloride salt.

(free base)

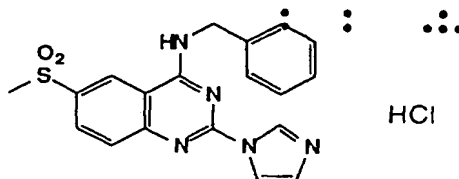
mp : 144-147°C

NMR (200MHz, DMSO-d<sub>6</sub>): d 2.85(s, 3H), 3.50(m, 4H), 3.70-3.90(m, 4H), 4.59(m, 1H), 7.11(s, 1H), 7.82(m, 1H), 7.98(s, 1H), 8.02(m, 1H), 8.62(s, 1H), 8.67(m, 1H), 9.14(t, 1H).

(2HCl salt)

mp : 190-192°C

NMR (200MHz, DMSO-d<sub>6</sub>): d 2.89(s, 3H), 3.51(s, 4H), 3.76(m, 2H), 3.89(m, 2H), 7.90(m, 2H), 8.14(m, 1H), 8.45(m, 1H), 8.89(m, 1H), 9.62(t, 1H), 10.10(m, 1H).



mp : 125-130°C.

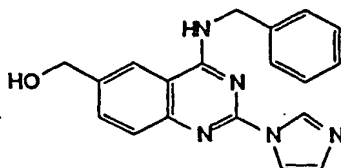
NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.34(s, 3H), 4.97(d, 2H), 7.31-7.50(m, 5H), 7.85(s, 1H), 7.93(d, 1H), 8.32(d, 1H), 8.44(s, 1H), 9.14(s, 1H), 9.98(s, 1H), 10.12(t, 1H).

IR (KBr): ν 3230(s), 3040(s), 2705(s), 2370(m), 1616(s), 1572(s), 1524(s), 1497(m), 1399(s), 1326(s), 1258(m), 1204(w), 1147(s), 1008(m), 834(w), 783(s), 730(w), 620(w), 535(m) cm<sup>-1</sup>.

Reference example 17(b)

6-hydroxymethyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline

[0258]



[0259] To a suspension of 0.68 g of the compound prepared in example 5(e) in 50 mL of anhydrous tetrahydrofuran was added 2 mL of 2M lithium borohydride in tetrahydrofuran. The reaction mixture was heated at reflux for two days. The mixture was then concentrated, diluted with water and the basic solution was acidified with 1N hydrochloric acid. The resulting solution was then basified with potassium carbonate, filtered and the solid washed with water and allowed to dry. The solid material was purified on silica gel column eluting with 5% methanol in chloroform. Obtained 85 mg of the desired product.

mp: 173°C (dec.).

NMR (200MHz, DMSO-d<sub>6</sub>):  $\delta$  4.67(d, 1H), 4.90(d, 1H), 5.47(t, 1H), 7.23(m, 1H), 7.25-7.51(m, 5H), 7.67-7.85(m, 2H), 8.12(m, 1H), 8.34(m, 1H), 8.91(s, 1H), 9.51 (t, 1H).

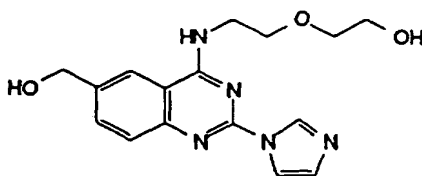
IR (KBr):  $\nu$  3445(mw), 2365(mw), 1599(s), 1559(m), 1505(mw), 1444(w), 1410(m), 1340(w), 1161(w), 1073(w) cm<sup>-1</sup>.

[0260] By the same procedure as described in Reference example 17(b), the below compound having the following physical data was given.

Example 16(b)

4-[2-(2-hydroxyethoxy)ethyl]amino-6-hydroxymethyl-2-(1-imidazolyl)-quinazoline

[0261]



mp : 183°C.

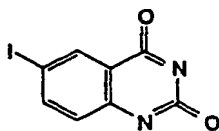
NMR (200MHz, DMSO-d<sub>6</sub>):  $\delta$  3.48(s, 4H), 3.76(m, 4H), 4.62(d, 2H), 5.44(t, 1H), 7.10(s, 1H), 7.62-7.80(m, 2H), 7.97 (s, 1H), 8.27(s, 1H), 8.60(s, 1H), 8.82(bs, 1H).

IR (KBr) :  $\nu$  3311(mw), 3156(w), 1597(s), 1558(w), 1487(w), 1438(w), 1408(ms), 1052(w) cm<sup>-1</sup>.

Reference example 18

6-iodoquinazolin-2,4-dione

[0262]

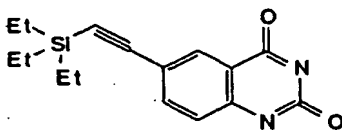


[0263] To a mixture of 25.36 g of 2-amino-5-iodobenzoic acid in 250 ml of water and 90 mL of THF was added 7.40 g of glacial acetic acid and stirred at room temperature. Then was added 7.82 g of potassium cyanate in water dropwise. Left to overnight. Added another 5.47 g of potassium cyanate. Stirred overnight. A total of 160 g of NaOH pellets were added portionwise; keeping the mixture cool in ice-water bath. The mixture was stirred at room temperature overnight. The mixture was cooled in a refrigerator and the precipitate filtered through a sintered glass funnel. The precipitate was then dissolved in water and acidified with 4N HCl. The precipitate was collected by filtration. The solid was dried in a vacuum oven to yield 25.44 g of the title compound.

Reference example 19

6-(2-triethylsilylethynyl)quinazolin-2,4-dione

[0264]



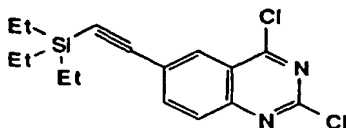
[0265] In a flask was placed 0.544 g of triphenylphosphine, 0.184 g of palladium chloride, and 5 mL of diethylamine. Stirred under a nitrogen atmosphere. To the resulting yellow mixture was added 75 mL of diethylamine, followed by 10.02 g of the compound prepared in reference example 18. Then added 19.8 mg of cuprous iodine to the purple suspension. Turned gray after 10 minutes. After 0.5 hr added 5.36 g of triethylsilyl acetylene and stirred at room temperature. After 3 hrs the solution turned purple. After another 1.5 hrs. the solution turned brown. Left to stir overnight. Monitored reaction by TLC. Removed the solvent under reduced pressure at 40 °C and added water. Acidified with 1N- HCl. The precipitated solid was collected by filtration, washed with water, and dried in a vacuum oven. The solid was then passed through a silica gel column, eluting with THF. After drying yielded 10.22 g of the title compound having the following physical data.

NMR (200 MHz, DMSO-d<sub>6</sub>):  $\delta$  0.65(dd, 6H), 0.93(dd, 9H), 7.15(d, 1H), 7.69(d, 1H), 11.38(br, 2H).

Reference example 20

2,4-dichloro-6-(2-triethylsilylethynyl)quinazoline

[0266]



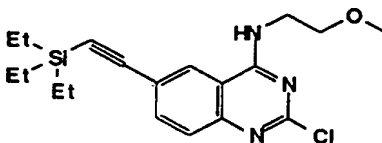
[0267] To 5.09 g of the compound prepared in reference example 19, was added 25 mL of  $\text{POCl}_3$  and warmed. Then added 1.03 g of N,N-dimethylaniline and heated to reflux. After 3.5 hrs, the excess  $\text{POCl}_3$  was removed under reduced pressure and the residue diluted in chloroform and poured slowly over ice. The organic layer was collected and the solvent removed. The residue was passed through a silica gel column using 20% EtOAc/hexane as a solvent. Yielded 1.4 g of the product having the following physical data.

NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.72(6H), 1.00(9H), 7.98(d, 1 H), 8.33(s, 1 H).

Reference example 21

2-chloro-4-(2-methoxyethyl)amino-6-(2-triethylsilylethynyl)quinazoline

[0268]



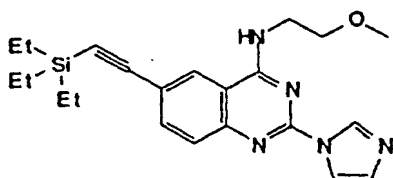
[0269] To 1.4 g of the compound prepared in reference example 20 in 20 mL of chloroform was added 2-methoxyethylamine and stirred at room temperature for 1.5 hr. Then added 4.2 ml of 1 N-NaOH and heated to reflux. Left to reflux overnight. The solvent was removed under reduced pressure and the residue taken up in chloroform and water. The organic layer was collected and dried over anhydrous potassium carbonate. Removal of solvent under reduced pressure yielded 1.44 g of the title compound.

NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.73 (m, 6H), 1.07(m, 9H), 3.45(s, 3H), 3.69(t, 2H), 3.88(dd, 2H), 6.32(br, 1H), 7.69(d, 1H), 7.78(dd, 1H), 7.80(s, 1H).

Example 17

2-(1-imidazolyl)-4-(2-methoxyethyl)amino-6-(2-triethylsilylethynyl)quinazoline

[0270]



[0271] To 1.32 g of the compound prepared in reference example 21 in 5 mL of ethanol was added excess imidazole

(0.93 g) and heated in an oil bath to 115 °C. After 1.5 hrs. removed from heat and diluted in chloroform and washed with 1N-NaOH, collected the organic layer and washed with water. The organic layer was extracted and dried over anhydrous potassium carbonate. Removal of solvent yielded 1.33 g of the title compound.

mp : 158-160 °C.

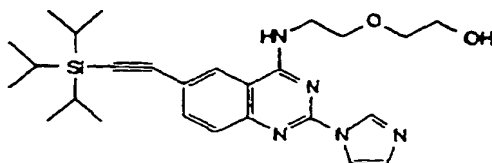
NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  0.70(q, 6H), 1.05(t, 9H), 3.30(s, 3H), 3.64(t, 2H), 3.81(dd, 2H), 7.10(s, 1H), 7.65(d, 1H), 7.78(dd, 1H), 7.96(s, 1H), 8.01 (s, 1H), 8.60(s, 1H), 8.95(br, 1H).

[0272] By the same procedures as described in reference examples 18, 19, 20 and 21, and example 17, the following compound was obtained.

#### Example 17(a)

2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-(2-triisopropylsilyl)ethynylquinazoline

[0273]



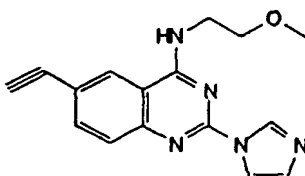
mp: 155-156 °C;

NMR (200MHz,  $CDCl_3$ ):  $\delta$  1.09 (s, 3H), 1.16 (s, 18H), 2.28 (br, 1H), 3.70 (m, 2H), 3.84 (dd, 4H), 3.95 (t, 2H), 6.65 (br, 1H), 7.14 (s, 1H), 7.68 (d, 1H), 7.75 (dd, 1 H), 7.87 (s, 1H), 7.93 (s, 1H), 8.65 (s, 1H).

#### Example 18

6-ethynyl-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline

[0274]



[0275] To 1.35 g of the compound prepared in example 17 in 20 mL of THF was added 3.3 mL of tetrabutylammonium fluoride (1 M in THF). Stirred at room temperature for 1.5 hrs. The excess THF was removed under reduced pressure and the residue taken up in chloroform and water. The insoluble precipitate was collected by filtration. Yielded 0.83 g of the title compound.

NMR (200MHz, DMSO- $d_6$ ):  $\delta$  .3.33(s, 1H), 3.66(m, 2H), 3.83(m, 2H), 4.34(s, 1H), 7.11(s, 1H), 7.65(d, 1 H), 7.82(dd, 1H), 7.96(s, 1H), 8.57(d, 1 H), 8.62(s, 1H), 8.90(broad, 1H).

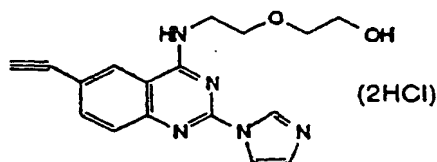
IR (KBr):  $\nu$  3290(s), 2945(m), 1606(s), 1559(s), 1451(s), 1352(s), 1106(s), 835(s)  $cm^{-1}$ .

[0276] By the same procedure as described in example 18, the following compound was given.

Example 18(a)

2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-ethynylquinazoline and its salt

[0277]



(free base)

mp : 166-167°C;

NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.50 (s, 4H), 3.78 (m, 4H), 4.35 (s, 1H), 4.59 (t, 1H), 7.10 (s, 1H), 7.65 (d, 1H), 7.80 (dd, 1H), 7.97 (s, 1H), 8.55 (d, 1H), 8.61 (s, 1H), 8.90 (br, 1H).

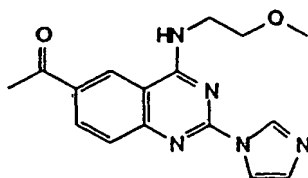
(HCl salt)

mp : 178 °C;

NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.51 (s, 4H), 3.87 (m, 2H), 4.44 (s, 1H), 7.73 (d, 1H), 7.82 (s, 1H), 7.90 (d, 1H), 8.40 (s, 1H), 8.67 (s, 1H), 9.25 (br, 1H).Example 19

6-acetyl-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline

[0278]



[0279] To 0.541 g of the compound prepared in example 18 in 10 ml of acetic acid was added 0.7 mL of 10% H<sub>2</sub>SO<sub>4</sub> and 0.10 g of mercury II sulfate and heated to reflux. After 2 hours removed from heat and basified. The yellow precipitate was filtered. The solid was washed with THF. Removed the solvent under reduced pressure and titrated the residue in 50 % ether/pentane. The solid was collected by filtration. Yielded 0.063 g of the desired product.

mp : 208-210 °C.

NMR (200MHz, CDCl<sub>3</sub>): δ 2.64(s, 1H), 3.49(s, 3H), 3.79(t, 2H), 3.95(q, 2H), 7.00(broad, 1H), 7.16(t, 1H), 7.74(d, 1H), 7.95(t, 1H), 8.17(dd, 1H), 8.42(d, 1H), 8.67(t, 1H).

[0280] By the same procedure as described in Example 19, the below compound having the following physical data was given.

Example 19(a)

4-[2-(2-hydroxyethoxy)ethyl]amino-6-acetyl-2-(1-imidazolyl)quinazoline

[0281]



mp 164-166°C.

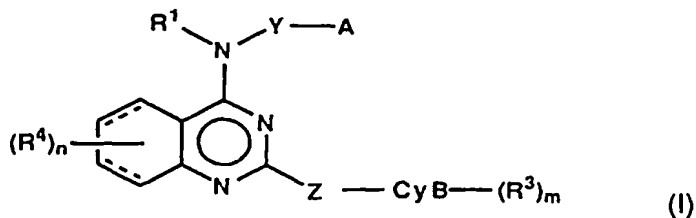
NMR (200MHz, DMSO-d<sub>6</sub>): δ 2.69(s, 3H), 3.51 (s, 4H), 3.76(m, 2H), 3.84(t, 2H), 4.60(br, 1H), 7.12(s, 1H), 7.73(d, 1H), 7.98(s, 1H), 8.27(dd, 1H), 8.64(s, 1H), 9.00(s, 1H), 9.25(br, 1H).IR (KBr) : ν 3350, 1671, 1623, 1593, 1558, 1474, 1447, 1418, 1365, 1307, 1270, 1111, 1051 cm<sup>-1</sup>.Formulation Example 1

[0282] The following components were admixed in conventional method and punched out to obtain 100 tablets each containing 50 mg of active ingredient.

4-phenylmethylamino-2-(3-pyridyl)quinazoline	5.0 g
cellulose calcium glycolate (disintegrating agent)	0.2 g
magnesium stearate (lubricating agent)	0.1 g
micro crystalline cellulose	4.7 g

Claims

1. A quinazoline derivative of the formula:



wherein

[1] ----- represents a single or double bond;

R¹ is hydrogen or C1-4 alkyl;

Y is C1-6 alkylene;

A is -O-R⁰ or -S(O)p-R⁰, in which R⁰ is hydroxy-C1-4 alkyl, p is 0-2;

Z is single bond, methylene, ethylene, vinylene or ethynylene;

CyB is

- (1) a 4-7 membered heteroaryl containing one nitrogen atom,  
 (2) a 4-7 membered heteroaryl containing two nitrogen atoms,  
 (3) a 4-7 membered heteroaryl containing three nitrogen atoms,  
 (4) a 4-7 membered heteroaryl containing one or two oxygen atoms,  
 (5) a 4-7 membered heteroaryl containing one or two sulfur atoms,

R<sup>3</sup> is hydrogen, C1-4 alkyl, C1-4 alkoxy, halogen or trifluoromethyl;  
 R<sup>4</sup> is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) -COOR<sup>8</sup>, in which R<sup>8</sup> is hydrogen or C1-4 alkyl, (5) -NR<sup>9</sup>R<sup>10</sup>, in which R<sup>9</sup> is hydrogen, C1-4 alkyl or phenyl(C1-4 alkyl) and R<sup>10</sup> is hydrogen or C1-4 alkyl, (6) -NHCOR<sup>11</sup>, in which R<sup>11</sup> is C1-4 alkyl, (7) -NHSO<sub>2</sub>R<sup>11</sup>, in which R<sup>11</sup> is as hereinbefore defined, (8) SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, in which R<sup>9</sup> and R<sup>10</sup> are as hereinbefore defined, (9) -OCOR<sup>11</sup>, in which R<sup>11</sup> is as hereinbefore defined, (10) halogen, (11) trifluoromethyl, (12) hydroxy, (13) nitro, (14) cyano, (15) -SO<sub>2</sub>N=CHNR<sup>12</sup>R<sup>13</sup> in which R<sup>12</sup> is hydrogen or C1-4 alkyl and R<sup>13</sup> is C1-4 alkyl, (16) -CONR<sup>14</sup>R<sup>15</sup> in which R<sup>14</sup> is hydrogen, C1-4 alkyl or phenyl(C1-4 alkyl) and R<sup>15</sup> is C1-4 alkyl, (17) C1-4 alkylthio, (18) C1-4 alkylsulfinyl, (19) C1-4 alkylsulfonyl, (20) ethynyl, (21) hydroxymethyl, (22) tri(C1-4 alkyl)silylethynyl or (23) acetyl;  
 m and n independently are 1 or 2;

[2] -----, R<sup>1</sup>, p, Z, CyB, R<sup>3</sup>, m, n are as hereinbefore defined;

Y is bond or C1-6 alkylene;  
 A is

- (i) -CyA-(R<sup>2</sup>)l, or  
 (ii) -O-R<sup>0</sup> or -S(O)<sub>p</sub>-R<sup>0</sup>,

in which R<sup>0</sup> is hydrogen, C1-4 alkyl or -CyA-(R<sup>2</sup>)l,  
 CyA is

- (1) a 3-7 membered, saturated or unsaturated carbocycle,  
 (2) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom,  
 (3) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom and one oxygen atom,  
 (4) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom and two oxygen atoms,  
 (5) a 4-7 membered, unsaturated or partially saturated heterocycle containing two nitrogen atoms and one oxygen atom,  
 (6) a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two sulfur atoms,  
 (7) a 4-7 membered, unsaturated, partially saturated or fully saturated heterocycle containing one or two oxygen atoms;

R<sup>2</sup> is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) -COOR<sup>5</sup>, in which R<sup>5</sup> is hydrogen or C1-4 alkyl, (5) -NR<sup>6</sup>R<sup>7</sup>, in which R<sup>6</sup> and R<sup>7</sup> independently are hydrogen or C1-4 alkyl, (6) -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, in which R<sup>6</sup> and R<sup>7</sup> are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro or (10) trifluoromethoxy;  
 l is 1 or 2;

when Z is methylene, ethylene, vinylene or ethynylene,

R<sup>4</sup> is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) -COOR<sup>8</sup>, in which R<sup>8</sup> is hydrogen or C1-4 alkyl, (5) -NR<sup>9</sup>R<sup>10</sup>, in which R<sup>9</sup> is hydrogen, C1-4 alkyl or phenyl(C1-4 alkyl) and R<sup>10</sup> is hydrogen or C1-4 alkyl, (6) -NHCOR<sup>11</sup>, in which R<sup>11</sup> is C1-4 alkyl, (7) -NHSO<sub>2</sub>R<sup>11</sup>, in which R<sup>11</sup> is as hereinbefore defined, (8) SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, in which R<sup>9</sup> and R<sup>10</sup> are as hereinbefore defined, (9) -OCOR<sup>11</sup>, in which R<sup>11</sup> is as hereinbefore defined, (10) halogen, (11) trifluoromethyl, (12) hydroxy, (13) nitro, (14) cyano, (15) -SO<sub>2</sub>N=CHNR<sup>12</sup>R<sup>13</sup> in which R<sup>12</sup> is hydrogen or C1-4 alkyl and R<sup>13</sup> is C1-4 alkyl, (16) -CONR<sup>14</sup>R<sup>15</sup> in which R<sup>14</sup> is hydrogen, C1-4 alkyl or phenyl(C1-4 alkyl) and R<sup>15</sup> is C1-4 alkyl, (17) C1-4 alkylthio, (18) C1-4 alkylsulfinyl, (19) C1-4 alkylsulfonyl, (20) ethynyl, (21) hydroxymethyl, (22) tri(C1-4 alkyl)silylethynyl or (23) acetyl;  
 when Z is single bond,

R<sup>4</sup> is (1) -NHSO<sub>2</sub>R<sup>11</sup>, in which R<sup>11</sup> is as hereinbefore defined, (2) SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, in which R<sup>9</sup> and R<sup>10</sup> are as hereinbefore defined, (3) -OCOR<sup>11</sup>, in which R<sup>11</sup> is as hereinbefore defined, (4) hydroxy, (5) -SO<sub>2</sub>N=CHNR<sup>12</sup>R<sup>13</sup> in which R<sup>12</sup> and R<sup>13</sup> are as hereinbefore defined, (6) -CONR<sup>14</sup>R<sup>15</sup> in which R<sup>14</sup> and R<sup>15</sup> are as hereinbefore defined, (7)



ethynyl, or (8) tri(C1-4 alkyl)silylethynyl;

[3] -----, R<sup>1</sup>, p, CyB, R<sup>3</sup>, m, n, CyA and I are as hereinbefore defined;

Y is bond or C1-6 alkylene;

A is

(i) -CyA-(R<sup>2</sup>)I, in which R<sup>2</sup> is (1) -NR<sup>6</sup>R<sup>7</sup>, in which R<sup>6</sup> and R<sup>7</sup> independently are hydrogen or C1-4 alkyl (with the proviso that R<sup>6</sup> and R<sup>7</sup> are not hydrogen at same time), (2) -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, in which R<sup>6</sup> and R<sup>7</sup> independently are hydrogen or C1-4 alkyl, or (3) trifluoromethoxy; or

(ii) -O-R<sup>0</sup>, in which R<sup>0</sup> is -CyA-(R<sup>2</sup>)I; or  
-S(O)<sub>p</sub>-R<sup>0</sup>, in which R<sup>0</sup> is hydrogen, C1-4 alkyl or -CyA-(R<sup>2</sup>)I;

in which R<sup>2</sup> is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) -COOR<sup>5</sup>, in which R<sup>5</sup> is hydrogen or C1-4 alkyl, (5) -NR<sup>6</sup>R<sup>7</sup>, in which R<sup>6</sup> and R<sup>7</sup> independently are hydrogen or C1-4 alkyl, (6) -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, in which R<sup>6</sup> and R<sup>7</sup> are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro or (10) trifluoromethoxy; Z is single bond;

R<sup>4</sup> is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) -COOR<sup>8</sup>, in which R<sup>8</sup> is hydrogen or C1-4 alkyl, (5) -NR<sup>9</sup>R<sup>10</sup>, in which R<sup>9</sup> is hydrogen, C1-4 alkyl or phenyl(C1-4 alkyl) and R<sup>10</sup> is hydrogen or C1-4 alkyl, (6) -NHCOR<sup>11</sup>, in which R<sup>11</sup> is C1-4 alkyl, (7) halogen, (8) trifluoromethyl, (9) nitro, (10) cyano, (11) C1-4 alkylthio, (12) C1-4 alkylsulfinyl, (13) C1-4 alkylsulfonyl, (14) hydroxymethyl or (15) acetyl; with the proviso that

(1) -CyA-(R<sup>2</sup>)I does not represent a cyclopentyl and trifluoromethylphenyl, when Y is a single bond;  
(2) CyB does not bond to Z through a nitrogen atom, when Z is vinylene or ethynylene;  
(3) CyB is not pyridine orthiophene when CyA is a 4-7 membered unsaturated, partially saturated or fully saturated heterocycle containing one or two oxygen atoms;  
(4) Y is not a single bond, when A is (ii) -O-R<sup>0</sup> or -S(O)<sub>p</sub>-R<sup>0</sup>;

or a compound which is:

- (1) 4-phenylmethylamino-2-(3-pyridyl)quinazoline,
- (2) 4-(3-methylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (3) 4-(3,4-dimethoxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (4) 4-(4-carboxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (5) 4-(3-chlorophenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (6) 4-(3-trifluoromethylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (7) 4-(3-nitrophenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (8) 4-phenylmethylamino-2-(6-chloro-3-pyridyl)quinazoline,
- (9) 4-phenylmethylamino-6-methyl-2-(3-pyridyl)quinazoline,
- (10) 4-phenylmethylamino-6,7-dimethoxy-2-(3-pyridyl)quinazoline,
- (11) 4-phenylmethylamino-6-acetylamino-2-(3-pyridyl)quinazoline,
- (12) 4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline,
- (13) 4-phenylmethylamino-6-bromo-2-(3-pyridyl)quinazoline,
- (14) 4-phenylmethylamino-7-fluoro-2-(3-pyridyl)quinazoline,
- (15) 4-phenylmethylamino-6-nitro-2-(3-pyridyl)quinazoline,
- (16) 4-phenylamino-2-(3-pyridyl)quinazoline,
- (17) 4-(3-methoxycarbonylphenyl)amino-2-(3-pyridyl)quinazoline,
- (18) 4-phenylethylamino-2-(3-pyridyl)quinazoline,
- (19) 4-phenylmethylamino-2-(2-pyridyl)quinazoline,
- (20) 4-phenylmethylamino-2-(4-pyridyl)quinazoline,
- (21) 6-iodo-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
- (22) 4-(3-carboxyphenyl)amino-2-(4-pyridyl)quinazoline,
- (23) 6-fluoro-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
- (24) 4-(cyclopropylmethyl)amino-2-(3-pyridyl)quinazoline,
- (25) 4-(3-pyridylmethyl)amino-2-(3-pyridyl)quinazoline,
- (26) 4-(2-thienylmethyl)amino-2-(3-pyridyl)quinazoline,
- (27) 4-(2-furylmethyl)amino-2-(1-imidazolyl)quinazoline,

- (28) 4-(2-tetrahydrofuranylmethyl)amino-2-(1-imidazolyl)quinazoline,  
 (29) 4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,  
 (30) 6-methoxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,  
 (31) 6-chloro-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,  
 (32) 4-(2-thienylmethyl)amino-2-(1-imidazolyl)quinazoline,  
 (33) 6-acetyl-4-(2-methoxyethyl)amino-2-(3-pyridyl)quinazoline,  
 (34) 4-phenylmethylamino-6-methoxy-2-(1-imidazolyl)quinazoline,  
 (35) 4-phenylmethylamino-6,7-dimethoxy-2-(1-imidazolyl)quinazoline,  
 (36) 4-phenylmethylamino-6-carboxy-2-(1-imidazolyl)quinazoline,  
 (37) 4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline,  
 (38) 4-phenylmethylamino-6-bromo-2-(1-imidazolyl)quinazoline,  
 (39) 4-phenylmethylamino-6-nitro-2-(1-imidazolyl)quinazoline,  
 (40) 4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 (41) 4-phenylmethylamino-2-(2-methyl-1-imidazolyl)quinazoline,  
 (42) 7-chloro-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 (43) 4-(3,4-dimethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline,  
 (44) 4-(2-phenylethyl)amino-2-(1-imidazolyl)quinazoline,  
 (45) 4-cyclohexylmethylamino-2-(1-imidazolyl)quinazoline,  
 (46) 6-iodo-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 (47) 4-phenylmethylamino-2-(1-triazolyl)quinazoline,  
 (48) 4-phenylmethylamino-6,8-diiodo-2-(1-imidazolyl)quinazoline,  
 (49) 4-phenylmethylamino-2-(2-thienyl)quinazoline,  
 (50) 4-phenylmethylamino-2-(2-furyl)quinazoline,  
 (51) 4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,  
 (52) 6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline, or  
 (53) 6-ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline;

or a pharmaceutically acceptable salt thereof or a hydrate thereof.

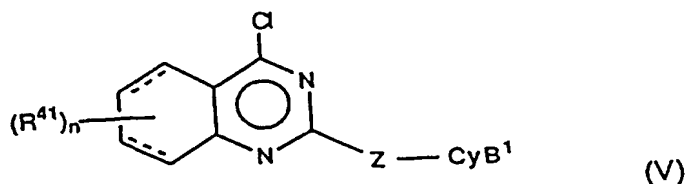
2. A compound according to claim 1, wherein CyB is a pyridine ring, an imidazole ring, a triazole or pyrrole ring, or a furan or thiophene ring.
3. A compound according to claim 1 or 2, wherein CyA is a benzene ring, a cyclopropyl ring, a cyclohexyl ring, a pyridine ring, a pyrrole or isoxazole ring, a thiophene ring, or a furan, tetrahydrofuran or pyran ring.
4. A compound according to claim 1 or 2 wherein A is OH, -O-C<sub>1-4</sub> alkyl, -O-C<sub>1-4</sub> alkyl-OH or -S(O)<sub>p</sub>-C<sub>1-4</sub> alkyl.
5. A compound according to any one of claims 1 to 4, wherein Y is a single bond, methylene or ethylene.
6. A compound according to any one of claims 1 to 5, wherein Z is a single bond, methylene or vinylene.
7. A compound according to any one of the preceding claims, which is:

- (1) 4-(4-(N,N-dimethylamino)phenylmethyl)amino-2-(3-pyridyl)quinazoline,  
 (2) 4-(4-sulfamoylphenylmethyl)amino-2-(3-pyridyl)quinazoline,  
 (3) 4-phenylmethylamino-2-(2-(3-pyridyl)vinyl)quinazoline,  
 (4) 4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,  
 (5) 6-chloro-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,  
 (6) 6-methoxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,  
 (7) 4-(2-(2-hydroxyethoxy)ethyl)amino-6-iodo-2-(1-imidazolyl)quinazoline,  
 (8) 4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylsulfinyl-2-(1-imidazolyl)-quinazoline,

- (9) 2-(1-imidazolyl)-4-(2-methoxyethyl)amino-6-(2-triethylsilylethynyl)quinazoline,  
 (10) 6-ethynyl-4-(2-methoxyethyl)amino-2-(3-pyridyl)quinazoline,  
 5 (11) 4-[2-(2-hydroxyethoxy)ethyl]amino-6-acetyl-2-(1-imidazolyl)quinazoline,  
 (12) 4-(2-methylthioethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,  
 (13) 4-(2-methylsulfinylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,  
 10 (14) 4-(2-methylsulfonylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,  
 (15) 4-[2-(2-hydroxyethoxy)ethyl]amino-6-methoxycarbonyl-2-(1-imidazolyl)-quinazoline,  
 15 (16) 4-[2-(2-hydroxyethoxy)ethyl]amino-6-hydroxymethyl-2-(1-imidazolyl)-quinazoline,  
 (17) 4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline,  
 (18) 2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-(2-triisopropyl-silylethynyl)-quinazoline,  
 20 (19) 2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-ethynylquinazoline,  
 (20) 4-phenylmethylamino-6-hydroxy-2-(1-imidazolyl)quinazoline,  
 25 (21) 4-phenylmethylamino-2-((1-imidazolyl)methyl)quinazoline,  
 (22) 6-chloro-4-phenylamino-2-(1-imidazolylmethyl)quinazoline,  
 (23) 6-chloro-4-phenylmethylamino-2-(1-imidazolylmethyl)quinazoline,  
 30 (24) 6-chloro-4-(3-carboxyphenyl)amino-2-(1-imidazolylmethyl)quinazoline,  
 (25) 6-dimethylaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 35 (26) 6-dimethylaminomethylideneaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 (27) 6-(phenylmethylaminosulfonyl)-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 (28) 4-(4-trifluoromethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline,  
 40 (29) 4-(3-trifluoromethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline 4-(3-trifluoromethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline  
 (30) 4-(2-phenoxyethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,  
 45 (31) 6-ethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,  
 (32) 4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline.

50 8. A process for the preparation of a 4-aminoquinazoline derivative of formula (I) as defined in claim 1, comprising:

- (a) reacting a compound of the formula:



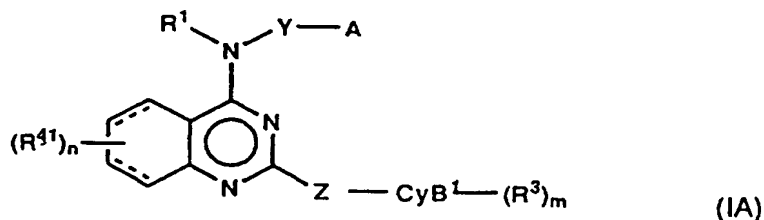
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wherein  $R^{41}$  is (1) hydrogen, (2)  $C_{1-4}$  alkyl, (3)  $C_{1-4}$  alkoxy, (4)  $-COOR^8$  wherein  $R^8$  is hydrogen or  $C_{1-4}$  alkyl, (5)  $-NR^9R^{10}$ , in which  $R^9$  and  $R^{10}$  are as hereinbefore defined, provided that  $R^9$  and  $R^{10}$  are not both hydrogen, (6)  $SO_2NR^9R^{10}$ , in which  $R^9$  and  $R^{10}$  are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro, (10) cyano, (11)  $C_{1-4}$  alkylthio, (12) tri( $C_{1-4}$  alkyl)silylethynyl, (13)  $-SO_2N=CHNR^{12}R^{13}$ , in which  $R^{12}$  is hydrogen or  $C_{1-4}$  alkyl and  $R^{13}$  is  $C_{1-4}$  alkyl or (14)  $-CONR^{14}R^{15}$ , in which  $R^{14}$  is hydrogen or  $C_{1-4}$  alkyl or phenyl( $C_{1-4}$  alkyl) and  $R^{15}$  is  $C_{1-4}$  alkyl,  $CyB^1$  is as defined in claim 1 for  $CyB$ , provided that  $CyB^1$  bonds to  $Z$  through a carbon atom in the  $CyB^1$  ring, and the other symbols are as defined in claim 1, with a compound of the formula:



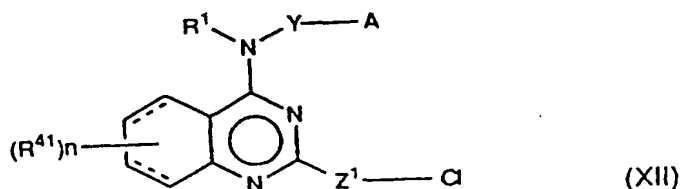
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wherein all the symbols are as defined in claim 1, to give a compound of the formula (IA):



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wherein  $R^{41}$  and  $CyB^1$  are as defined above and the other symbols are as defined in claim 1;  
(b) reacting a compound of the formula:

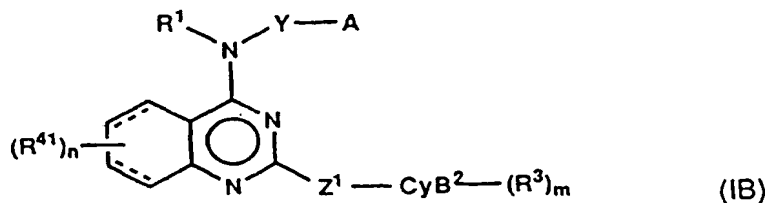


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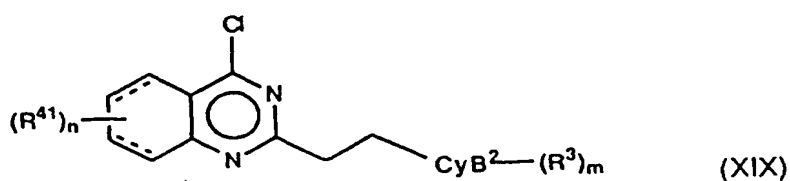
wherein  $R^{41}$  is as defined above,  $Z^1$  is a single bond or methylene, and the other symbols are as defined in claim 1, with a compound of the formula:



wherein  $\text{CyB}^2$  is as defined in claim 1 for  $\text{CyB}$ , provided that  $\text{CyB}^2$  bonds to  $\text{Z}^1$  through a nitrogen atom in the  $\text{CyB}^2$  ring, and the other symbols are as defined in claim 1, to give a compound of the formula (IB):



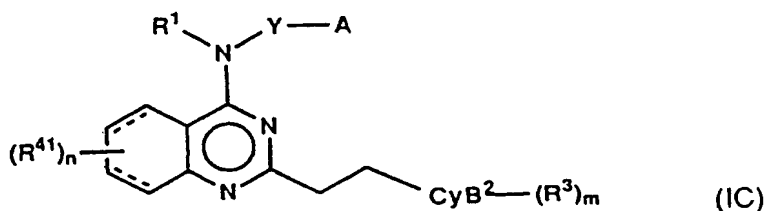
15 wherein  $\text{R}^{41}$ ,  $\text{Z}$  and  $\text{CyB}^2$  are as defined above and the other symbols are as defined in claim 1; or  
(c) reacting a compound of the formula:



30 wherein  $\text{R}^{41}$  and  $\text{CyB}^2$  are as defined above and the other symbols are as defined in claim 1 with a compound of the formula:



40 wherein all the symbols are as defined in claim 1, to give a compound of the formula (IC):



55 wherein  $\text{R}^{41}$  and  $\text{CyB}^2$  are as defined above and the other symbols are as defined in claim 1; and optionally converting the compound of formula (I) thus obtained into another compound of formula (I).

9. A pharmaceutical composition for the treatment of mammals, including humans, comprising as active ingredient, an effective amount of a compound of the formula (I), a pharmaceutically acceptable salt thereof or a hydrate

thereof in association with a pharmaceutically acceptable carrier or coating.

10. A compound of the formula (I) as defined in claim 1, a pharmaceutically acceptable salt thereof or a hydrate thereof, for use as a medicament in the treatment of mammals.

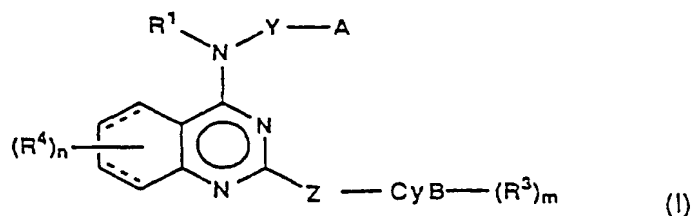
11. A compound according to claim 1, which is:

- (1) 4-phenylmethylamino-2-(3-pyridyl)quinazoline,
- (2) 4-(3-methylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (3) 4-(3,4-dimethoxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (4) 4-(4-carboxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (5) 4-(3-chlorophenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (6) 4-(3-trifluoromethylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (7) 4-(3-nitrophenylmethyl)amino-2-(3-pyridyl)quinazoline,
- (8) 4-phenylmethylamino-2-(6-chloro-3-pyridyl)quinazoline,
- (9) 4-phenylmethylamino-6-methyl-2-(3-pyridyl)quinazoline,
- (10) 4-phenylmethylamino-6,7-dimethoxy-2-(3-pyridyl)quinazoline,
- (11) 4-phenylmethylamino-6-acetylamino-2-(3-pyridyl)quinazoline,
- (12) 4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline,
- (13) 4-phenylmethylamino-6-bromo-2-(3-pyridyl)quinazoline,
- (14) 4-phenylmethylamino-7-fluoro-2-(3-pyridyl)quinazoline,
- (15) 4-phenylmethylamino-6-nitro-2-(3-pyridyl)quinazoline,
- (16) 4-phenylamino-2-(3-pyridyl)quinazoline,
- (17) 4-(3-methoxycarbonylphenyl)amino-2-(3-pyridyl)quinazoline,
- (18) 4-phenylethylamino-2-(3-pyridyl)quinazoline,
- (19) 4-phenylmethylamino-2-(2-pyridyl)quinazoline,
- (20) 4-phenylmethylamino-2-(4-pyridyl)quinazoline,
- (21) 6-iodo-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
- (22) 4-(3-carboxyphenyl)amino-2-(4-pyridyl)quinazoline,
- (23) 6-fluoro-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
- (24) 4-(cyclopropylmethyl)amino-2-(3-pyridyl)quinazoline,
- (25) 4-(3-pyridylmethyl)amino-2-(3-pyridyl)quinazoline,
- (26) 4-(2-thienylmethyl)amino-2-(3-pyridyl)quinazoline,
- (27) 4-(2-furylmethyl)amino-2-(1-imidazolyl)quinazoline,
- (28) 4-(2-tetrahydrofuran-2-ylmethyl)amino-2-(1-imidazolyl)quinazoline,
- (29) 4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,
- (30) 6-methoxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,
- (31) 6-chloro-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,
- (32) 4-(2-thienylmethyl)amino-2-(1-imidazolyl)quinazoline,
- (33) 6-acetyl-4-(2-methoxyethyl)amino-2-(3-pyridyl)quinazoline,
- (34) 4-phenylmethylamino-6-methoxy-2-(1-imidazolyl)quinazoline,
- (35) 4-phenylmethylamino-6,7-dimethoxy-2-(1-imidazolyl)quinazoline,
- (36) 4-phenylmethylamino-6-carboxy-2-(1-imidazolyl)quinazoline,
- (37) 4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline,
- (38) 4-phenylmethylamino-6-bromo-2-(1-imidazolyl)quinazoline,
- (39) 4-phenylmethylamino-6-nitro-2-(1-imidazolyl)quinazoline,
- (40) 4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
- (41) 4-phenylmethylamino-2-(2-methyl-1-imidazolyl)quinazoline,
- (42) 7-chloro-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
- (43) 4-(3,4-dimethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline,
- (44) 4-(2-phenylethyl)amino-2-(1-imidazolyl)quinazoline,
- (45) 4-cyclohexylmethylamino-2-(1-imidazolyl)quinazoline,
- (46) 6-iodo-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
- (47) 4-phenylmethylamino-2-(1-triazolyl)quinazoline,
- (48) 4-phenylmethylamino-6,8-diiodo-2-(1-imidazolyl)quinazoline,
- (49) 4-phenylmethylamino-2-(2-thienyl)quinazoline,
- (50) 4-phenylmethylamino-2-(2-furyl)quinazoline,
- (51) 4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,

(52) 6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline, or  
 (53) 6-ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline.

## Patentansprüche

### 1. Chinazolinderivat der Formel:



worin

[1] ----- eine Einfach- oder Doppelbindung bedeutet;

R¹ Wasserstoff oder C<sub>1-4</sub>-Alkyl;

Y C<sub>1-6</sub>-Alkylen ist;

A -O-R⁰ oder -S(O)<sub>p</sub>-R⁰ mit R⁰ gleich Hydroxy-C<sub>1-4</sub>-alkyl und p gleich 0 - 2 ist;

Z eine Einfachbindung, Methylen, Ethylen, Vinylen oder Ethinylen bedeutet;

CyB

(1) ein 4- bis 7-gliedriges Heteroaryl, das ein Stickstoffatom enthält,

(2) ein 4- bis 7-gliedriges Heteroaryl, das zwei Stickstoffatome enthält,

(3) ein 4- bis 7-gliedriges Heteroaryl, das drei Stickstoffatome enthält,

(4) ein 4- bis 7-gliedriges Heteroaryl, das ein oder zwei Sauerstoffatome enthält,

(5) ein 4- bis 7-gliedriges Heteroaryl, das ein oder zwei Schwefelatome enthält, ist;

R³ Wasserstoff, C<sub>1-4</sub>-Alkyl, C<sub>1-4</sub>-Alkoxy, Halogen oder Trifluormethyl bedeutet;

R⁴ (1) Wasserstoff, (2) C<sub>1-4</sub>-Alkyl, (3) C<sub>1-4</sub>-Alkoxy, (4) -COOR⁸ mit R⁸ gleich Wasserstoff oder C<sub>1-4</sub>-Alkyl, (5) -NR⁹R¹⁰ mit R⁹ gleich Wasserstoff, C<sub>1-4</sub>-Alkyl oder Phenyl(C<sub>1-4</sub>-alkyl) und R¹⁰ gleich Wasserstoff oder C<sub>1-4</sub>-Alkyl

(6) -NHCOR¹¹ mit R¹¹ gleich C<sub>1-4</sub>-Alkyl, (7) -NHSO₂R¹¹ mit R¹¹ gleich der vorhergehenden Definition, (8) SO₂NR⁹R¹⁰ mit R⁹ und R¹⁰ gleich der vorhergehenden Definition, (9) -OCOR¹¹ mit R¹¹ gleich der vorhergehenden Definition, (10) Halogen, (11) Trifluormethyl, (12) Hydroxy, (13) Nitro, (14) Cyano, (15) -SO₂N=CHNR¹²R¹³ mit R¹² gleich Wasserstoff oder C<sub>1-4</sub>-Alkyl und R¹³ gleich C<sub>1-4</sub>-Alkyl, (16) -CONR¹⁴R¹⁵ mit R¹⁴ gleich Wasserstoff, C<sub>1-4</sub>-Alkyl oder Phenyl(C<sub>1-4</sub>-alkyl) und

R¹⁵ gleich C<sub>1-4</sub>-Alkyl, (17) C<sub>1-4</sub>-Alkylthio, (18) C<sub>1-4</sub>-Alkylsulfinyl, (19) C<sub>1-4</sub>-Alkylsulfonyl, (20) Ethinyl, (21) Hydroxymethyl, (22) Tri(C<sub>1-4</sub>-alkyl)silylethinyl oder (23) Acetyl bedeutet;

m und n unabhängig voneinander 1 oder 2 sind;

[2] -----, R¹, p, Z, CyB, R³, m, n wie zuvor definiert sind;

Y eine Bindung oder C<sub>1-6</sub>-Alkylen ist;

A

(i) -CyA-(R²)<sub>1</sub> oder

(ii) -O-R⁰ oder -S(O)<sub>p</sub>-R⁰,

worin

R⁰ Wasserstoff, C<sub>1-4</sub>-Alkyl oder -CyA-(R²)<sub>1</sub> ist,

CyA

- (1) ein 3- bis 7-gliedriger gesättigter oder ungesättigter Carbocyclus,  
 (2) ein 4- bis 7-gliedriger ungesättigter oder partiell gesättigter Heterocyclus, der ein Stickstoffatom enthält,  
 (3) ein 4- bis 7-gliedriger ungesättigter oder partiell gesättigter Heterocyclus, der ein Stickstoffatom und ein Sauerstoffatom enthält,  
 (4) ein 4- bis 7-gliedriger ungesättigter oder partiell gesättigter Heterocyclus, der ein Stickstoffatom und zwei Sauerstoffatome enthält,  
 (5) ein 4- bis 7-gliedriger ungesättigter oder partiell gesättigter Heterocyclus, der zwei Stickstoffatome und ein Sauerstoffatom enthält,  
 (6) ein 4- bis 7-gliedriger ungesättigter oder partiell gesättigter Heterocyclus, der ein oder zwei Schwefelatome enthält,  
 (7) ein 4- bis 7-gliedriger ungesättigter oder partiell gesättigter oder vollständig gesättigter Heterocyclus, der ein oder zwei Sauerstoffatome enthält, ist;

R<sup>2</sup> (1) Wasserstoff, (2) C<sub>1-4</sub>-Alkyl, (3) C<sub>1-4</sub>-Alkoxy, (4) -COOR<sup>5</sup> mit R<sup>5</sup> gleich Wasserstoff oder C<sub>1-4</sub>-Alkyl, (5) -NR<sup>6</sup>R<sup>7</sup> mit R<sup>6</sup> und R<sup>7</sup> unabhängig voneinander gleich Wasserstoff oder C<sub>1-4</sub>-Alkyl, (6) -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup> mit R<sup>6</sup> und R<sup>7</sup> gleich der vorhergehenden Definition, (7) Halogen, (8) Trifluormethyl, (9) Nitro oder (10) Trifluormethoxy ist;

I 1 oder 2 ist, bedeutet;

im Falle von Z gleich Methylen, Ethylen, Vinylen oder Ethinylen

R<sup>4</sup> (1) Wasserstoff, (2) C<sub>1-4</sub>-Alkyl, (3) C<sub>1-4</sub>-Alkoxy, (4) -COOR<sup>8</sup> mit R<sup>8</sup> gleich Wasserstoff oder C<sub>1-4</sub>-Alkyl, (5) -NR<sup>9</sup>R<sup>10</sup> mit R<sup>9</sup> gleich Wasserstoff, C<sub>1-4</sub>-Alkyl oder Phenyl(C<sub>1-4</sub>-alkyl) und R<sup>10</sup> gleich Wasserstoff oder C<sub>1-4</sub>-Alkyl, (6) -NHCOR<sup>11</sup> mit R<sup>11</sup> gleich C<sub>1-4</sub>-Alkyl, (7) -NHSO<sub>2</sub>R<sup>11</sup> mit R<sup>11</sup> gleich der vorhergehenden Definition, (8) SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup> mit R<sup>9</sup> und R<sup>10</sup> gleich der vorhergehenden Definition, (9) -OCOR<sup>11</sup> mit R<sup>11</sup> gleich der vorhergehenden Definition, (10) Halogen, (11) Trifluormethyl, (12) Hydroxy, (13) Nitro, (14) Cyano, (15) -SO<sub>2</sub>N=CHNR<sup>12</sup>R<sup>13</sup> mit R<sup>12</sup> gleich Wasserstoff oder C<sub>1-4</sub>-Alkyl und R<sup>13</sup> gleich C<sub>1-4</sub>-Alkyl, (16) -CONR<sup>14</sup>R<sup>15</sup> mit R<sup>14</sup> gleich Wasserstoff, C<sub>1-4</sub>-Alkyl oder Phenyl(C<sub>1-4</sub>-alkyl) und R<sup>15</sup> gleich C<sub>1-4</sub>-Alkyl, (17) C<sub>1-4</sub>-Alkylthio, (18) C<sub>1-4</sub>-Alkylsulfanyl, (19) C<sub>1-4</sub>-Alkylsulfonyl, (20) Ethinyl, (21) Hydroxymethyl, (22) Tri(C<sub>1-4</sub>-alkyl) silylethynyl oder (23) Acetyl bedeutet;

im Falle von Z gleich einer Einfachbindung

R<sup>4</sup> (1) -NHSO<sub>2</sub>R<sup>11</sup> mit R<sup>11</sup> gleich der vorhergehenden Definition, (2) SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup> mit R<sup>9</sup> und R<sup>10</sup> gleich der vorhergehenden Definition, (3) -OCOR<sup>11</sup> mit R<sup>11</sup> gleich der vorhergehenden Definition, (4) Hydroxy, (5) -SO<sub>2</sub>N=CHNR<sup>12</sup>R<sup>13</sup> mit R<sup>12</sup> und R<sup>13</sup> gleich der vorhergehenden Definition, (6) -CONR<sup>14</sup>R<sup>15</sup> mit R<sup>14</sup> und R<sup>15</sup> gleich der vorhergehenden Definition, (7) Ethinyl oder (8) Tri (C<sub>1-4</sub>-alkyl) silylethynyl bedeutet;

[3] -----, R<sup>1</sup>, p, CyB, R<sup>3</sup>, m, n, CyA und 1 wie zuvor definiert sind;

Y eine Bindung oder C<sub>1-6</sub>-Alkylen ist;

A

(i) -CyA-(R<sup>2</sup>)<sub>1</sub>, worin R<sup>2</sup> (1) -NR<sup>6</sup>R<sup>7</sup> mit R<sup>6</sup> und R<sup>7</sup> unabhängig voneinander gleich Wasserstoff oder C<sub>1-4</sub>-Alkyl (wobei R<sup>6</sup> und R<sup>7</sup> nicht gleichzeitig Wasserstoff sind), (2) -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup> mit R<sup>6</sup> und R<sup>7</sup> unabhängig voneinander gleich Wasserstoff oder C<sub>1-4</sub>-Alkyl oder (3) Trifluormethoxy ist; oder

(ii) -O-R<sup>0</sup> mit R<sup>0</sup> gleich -CyA-(R<sup>2</sup>)<sub>1</sub> oder

-S(O)<sub>p</sub>-R<sup>0</sup> mit R<sup>0</sup> gleich Wasserstoff, C<sub>1-4</sub>-Alkyl oder

-CyA-(R<sup>2</sup>)<sub>1</sub>,

worin R<sup>2</sup> (1) Wasserstoff, (2) C<sub>1-4</sub>-Alkyl, (3) C<sub>1-4</sub>-Alkoxy, (4) -COOR<sup>5</sup> mit R<sup>5</sup> gleich Wasserstoff oder C<sub>1-4</sub>-Alkyl, (5) -NR<sup>6</sup>R<sup>7</sup> mit R<sup>6</sup> und R<sup>7</sup> unabhängig voneinander gleich Wasserstoff oder C<sub>1-4</sub>-Alkyl, (6) -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup> mit R<sup>6</sup> und R<sup>7</sup> gleich der vorhergehenden Definition, (7) Halogen, (8) Trifluormethyl, (9) Nitro oder (10) Trifluormethoxy ist, bedeutet; Z eine Einfachbindung ist;

R<sup>4</sup> (1) Wasserstoff, (2) C<sub>1-4</sub>-Alkyl, (3) C<sub>1-4</sub>-Alkoxy, (4) -COOR<sup>8</sup> mit R<sup>8</sup> gleich Wasserstoff oder C<sub>1-4</sub>-Alkyl, (5) -NR<sup>9</sup>R<sup>10</sup> mit R<sup>9</sup> gleich Wasserstoff, C<sub>1-4</sub>-Alkyl oder Phenyl(C<sub>1-4</sub>-alkyl) und R<sup>10</sup> gleich Wasserstoff oder C<sub>1-4</sub>-Alkyl, (6) -NHCOR<sup>11</sup> mit R<sup>11</sup> gleich C<sub>1-4</sub>-Alkyl, (7) Halogen, (8) Trifluormethyl, (9) Nitro, (10) Cyano, (11) C<sub>1-4</sub>-Alkylthio, (12) C<sub>1-4</sub>-Alkylsulfanyl, (13) C<sub>1-4</sub>-Alkylsulfonyl, (14) Hydroxymethyl oder (15) Acetyl bedeutet;



unter dem Vorbehalt, dass

- (1) -CyA-(R<sup>2</sup>)<sub>1</sub> nicht für ein Cyclopentyl und Trifluormethylphenyl steht, wenn Y eine Einfachbindung ist;  
 (2) CyB nicht über ein Stickstoffatom an Z gebunden ist, wenn Z Vinylen ode Ethinylen ist;  
 (3) CyB nicht Pyridin oder Thiophen ist, wenn CyA ein 4- bis 7-gliedriger ungesättigter, partiell gesättigter oder vollständig gesättigter Heterocyclus, der ein oder zwei Sauerstoffatome enthält, ist;  
 (4) Y keine Einfachbindung ist, wenn A (ii) -O-R<sup>0</sup> oder -S(O)<sub>p</sub>-R<sup>0</sup> ist;

oder eine Verbindung, die da ist:

- (1) 4-Phenylmethylamino-2-(3-pyridyl)chinazolin,  
 (2) 4-(3-Methylphenylmethyl)amino-2-(3-pyridyl)chinazolin,  
 (3) 4-(3,4-Dimethoxyphenylmethyl)amino-2-(3-pyridyl)-chinazolin,  
 (4) 4-(4-Carboxyphenylmethyl)amino-2-(3-pyridyl)-chinazolin,  
 (5) 4-(3-Chlorphenylmethyl)amino-2-(3-pyridyl)chinazolin,  
 (6) 4-(3-Trifluormethylphenylmethyl)amino-2-(3-pyridyl)-chinazolin,  
 (7) 4-(3-Nitrophenylmethyl)amino-2-(3-pyridyl)chinazolin,  
 (8) 4-Phenylmethylamino-2-(6-chlor-3-pyridyl)chinazolin,  
 (9) 4-Phenylmethylamino-6-methyl-2-(3-pyridyl)chinazolin,  
 (10) 4-Phenylmethylamino-6,7-dimethoxy-2-(3-pyridyl)-chinazolin,  
 (11) 4-Phenylmethylamino-6-acetylamino-2-(3-pyridyl)-chinazolin,  
 (12) 4-Phenylmethylamino-6-chlor-2-(3-pyridyl)chinazolin,  
 (13) 4-Phenylmethylamino-6-brom-2-(3-pyridyl)chinazolin,  
 (14) 4-Phenylmethylamino-7-fluor-2-(3-pyridyl)chinazolin,  
 (15) 4-Phenylmethylamino-6-nitro-2-(3-pyridyl)chinazolin,  
 (16) 4-Phenylamino-2-(3-pyridyl)chinazolin,  
 (17) 4-(3-Methoxycarbonylphenyl)amino-2-(3-pyridyl)-chinazolin,  
 (18) 4-Phenylethylamino-2-(3-pyridyl)chinazolin,  
 (19) 4-Phenylmethylamino-2-(2-pyridyl)chinazolin,  
 (20) 4-Phenylmethylamino-2-(4-pyridyl)chinazolin,  
 (21) 6-Iod-4-phenylmethylamino-2-(3-pyridyl)chinazolin,  
 (22) 4-(3-Carboxyphenyl)amino-2-(4-pyridyl)chinazolin,  
 (23) 6-Fluor-4-phenylmethylamino-2-(3-pyridyl)chinazolin,  
 (24) 4-(Cyclopropylmethyl)amino-2-(3-pyridyl)chinazolin,  
 (25) 4-(3-Pyridylmethyl)amino-2-(3-pyridyl)chinazolin,  
 (26) 4-(2-Thienylmethyl)amino-2-(3-pyridyl)chinazolin,  
 (27) 4-(2-Furylmethyl)amino-2-(1-imidazolyl)chinazolin,  
 (28) 4-(2-Tetrahydrofuranlylmethyl)amino-2-(1-imidazolyl)-chinazolin,  
 (29) 4-(4-Tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-chinazolin,  
 (30) 6-Methoxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)chinazolin,  
 (31) 6-Chlor-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)chinazolin,  
 (32) 4-(2-Thienylmethyl)amino-2-(1-imidazolyl)chinazolin,  
 (33) 6-Acetyl-4-(2-methoxyethyl)amino-2-(3-pyridyl)-chinazolin,  
 (34) 4-Phenylmethylamino-6-methoxy-2-(1-imidazolyl)-chinazolin,  
 (35) 4-Phenylmethylamino-6,7-dimethoxy-2-(1-imidazolyl)-chinazolin,  
 (36) 4-Phenylmethylamino-6-carboxy-2-(1-imidazolyl)-chinazolin,  
 (37) 4-Phenylmethylamino-6-chlor-2-(1-imidazolyl)-chinazolin,  
 (38) 4-Phenylmethylamino-6-brom-2-(1-imidazolyl)chinazolin,  
 (39) 4-Phenylmethylamino-6-nitro-2-(1-imidazolyl)-chinazolin,  
 (40) 4-Phenylmethylamino-2-(1-imidazolyl)chinazolin,  
 (41) 4-Phenylmethylamino-2-(2-methyl-1-imidazolyl)-chinazolin,  
 (42) 7-Chlor-4-phenylmethylamino-2-(1-imidazolyl)-chinazolin,  
 (43) 4-(3,4-Dimethoxyphenylmethyl)amino-2-(1-imidazolyl)-chinazolin,  
 (44) 4-(2-Phenylethyl)amino-2-(1-imidazolyl)chinazolin,  
 (45) 4-Cyclohexylmethylamino-2-(1-imidazolyl)chinazolin,  
 (46) 6-Iod-4-phenylmethylamino-2-(1-imidazolyl)chinazolin,  
 (47) 4-Phenylmethylamino-2-(1-triazolyl)-chinazolin,

- (48) 4-Phenylmethylamino-6,8-diiod-2-(1-imidazolyl)-chinazolin,  
 (49) 4-Phenylmethylamino-2-(2-thienyl)chinazolin,  
 (50) 4-Phenylmethylamino-2-(2-furyl)chinazolin,  
 (51) 4-Phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydrochinazolin,  
 (52) 6-Carboxy-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydrochinazolin oder  
 (53) 6-Ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydrochinazolin

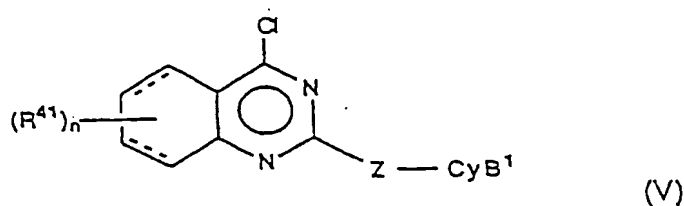
oder ein pharmazeutisch akzeptables Salz derselben oder ein Hydrat derselben.

2. Verbindung gemäß Anspruch 1, worin CyB ein Pyridinring, ein Imidazolring, ein Triazol- oder Pyrrolring oder ein Furan- oder Thiophenring ist.
3. Verbindung gemäß den Ansprüchen 1 oder 2, worin CyA ein Benzolring, ein Cyclopropylring, ein Cyclohexylring, ein Pyridinring, ein Pyrrol- oder Isoxazolring, ein Thiophenring oder ein Furan-, Tetrahydrofuran- oder Pyranring ist.
4. Verbindung gemäß den Ansprüchen 1 oder 2, worin A OH, -O-C<sub>1-4</sub>-Alkyl, -O-C<sub>1-4</sub>-Alkyl-OH oder -S(O)<sub>p</sub>-C<sub>1-4</sub>-Alkyl ist.
5. Verbindung gemäß einem der Ansprüche 1 bis 4, worin Y eine Einfachbindung, Methylen oder Ethylen ist.
6. Verbindung gemäß einem der Ansprüche 1 bis 5, worin Z eine Einfachbindung, Methylen oder Vinylen ist.
7. Verbindung gemäß einem der vorhergehenden Ansprüche, die da ist:

- (1) 4-(4-(N,N-Dimethylamino)phenylmethyl)amino-2-(3-pyridyl)chinazolin,  
 (2) 4-(4-Sulfamoylphenylmethyl)amino-2-(3-pyridyl)-chinazolin,  
 (3) 4-Phenylmethylamino-2-(2-(3-pyridyl)vinyl)chinazolin,  
 (4) 4-(2-Phenoxyethyl)amino-2-(1-imidazolyl)chinazolin,  
 (5) 6-Chlor-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)chinazolin,  
 (6) 6-Methoxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)chinazolin,  
 (7) 4-(2-(2-Hydroxyethoxy)ethyl)amino-6-iod-2-(1-imidazolyl)chinazolin,  
 (8) 4-(2-(2-Hydroxyethoxy)ethyl)amino-6-methylsulfinyl-2-(1-imidazolyl)chinazolin,  
 (9) 2-(1-Imidazolyl)-4-(2-methoxyethyl)amino-6-(2-triethylsilylethynyl)chinazolin,  
 (10) 6-Ethynyl-4-(2-methoxyethyl)amino-2-(3-pyridyl)chinazolin,  
 (11) 4-[2-(2-Hydroxyethoxy)ethyl]amino-6-acetyl-2-(1-imidazolyl)chinazolin,  
 (12) 4-(2-Methylthioethyl)amino-6-methoxy-2-(1-imidazolyl)-chinazolin,  
 (13) 4-(2-Methylsulfinylethyl)amino-6-methoxy-2-(1-imidazolyl)chinazolin,  
 (14) 4-(2-Methylsulfonylethyl)amino-6-methoxy-2-(1-imidazolyl)chinazolin,  
 (15) 4-[2-(2-Hydroxyethoxy)ethyl]amino-6-methoxycarbonyl-2-(1-imidazolyl)chinazolin,  
 (16) 4-[2-(2-Hydroxyethoxy)ethyl]amino-6-hydroxymethyl-2-(1-imidazolyl)chinazolin,  
 (17) 4-(2-(2-Hydroxyethoxy)ethyl)amino-6-methylthio-2-(1-imidazolyl)chinazolin,  
 (18) 2-(1-Imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-(2-triisopropylsilylethynyl)chinazolin,  
 (19) 2-(1-Imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-ethynylchinazolin,  
 (20) 4-Phenylmethylamino-6-hydroxy-2-(1-imidazolyl)-chinazolin,  
 (21) 4-Phenylmethylamino-2-((1-imidazolyl)methyl)-chinazolin,  
 (22) 6-Chlor-4-phenylamino-2-(1-imidazolylmethyl)-chinazolin,  
 (23) 6-Chlor-4-phenylmethylamino-2-(1-imidazolylmethyl)-chinazolin,  
 (24) 6-Chlor-4-(3-carboxyphenyl)amino-2-(1-imidazolylmethyl)chinazolin,  
 (25) 6-Dimethylaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)chinazolin,  
 (26) 6-Dimethylaminomethylidenaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)chinazolin,  
 (27) 6-(Phenylmethylaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)chinazolin,  
 (28) 4-(4-Trifluormethoxyphenylmethyl)amino-2-(1-imidazolyl)chinazolin,  
 (29) 4-(3-Trifluormethoxyphenylmethyl)amino-2-(1-imidazolyl)chinazolin,  
 (30) 4-(2-Phenoxyethyl)amino-6-methoxy-2-(1-imidazolyl)-chinazolin,  
 (31) 6-Ethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydrochinazolin oder  
 (32) 4-(2-(2-Hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-5,6,7,8-tetrahydrochinazolin.

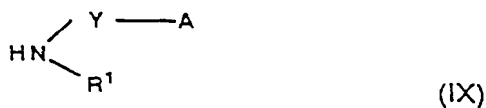
8. Verfahren zur Herstellung eines 4-Aminochinazolinderivats der Formel (I) gemäß Anspruch 1 durch:

(a) Umsetzen einer Verbindung der Formel:

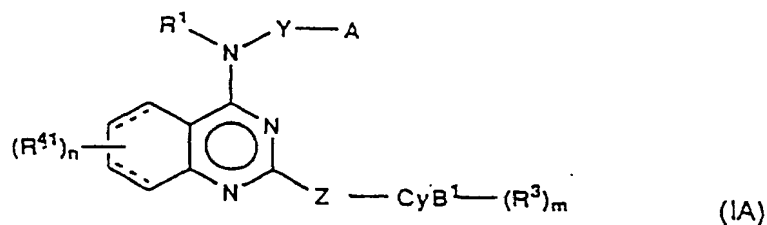


15 worin  $R^{41}$  (1) Wasserstoff, (2)  $C_{1-4}$ -Alkyl, (3)  $C_{1-4}$ -Alkoxy, (4)  $-COOR^8$  mit  $R^8$  gleich Wasserstoff oder  $C_{1-4}$ -Alkyl, (5)  $-NR^9R^{10}$  mit  $R^9$  und  $R^{10}$  gleich der vorhergehenden Definition, wobei  $R^9$  und  $R^{10}$  nicht beide Wasserstoff sind, (6)  $SO_2NR^9R^{10}$  mit  $R^9$  und  $R^{10}$  gleich der vorhergehenden Definition, (7) Halogen, (8) Trifluormethyl, (9) Nitro, (10) Cyano, (11)  $C_{1-4}$ -Alkylthio, (12)  $Tri(C_{1-4}\text{-alkyl})\text{silylethynyl}$ , (13)  $-SO_2N=CHNR^{12}R^{13}$  mit  $R^{12}$  gleich Wasserstoff oder  $C_{1-4}$ -Alkyl und  $R^{13}$  gleich  $C_{1-4}$ -Alkyl oder (14)  $-CONR^{14}R^{15}$  mit  $R^{14}$  gleich Wasserstoff oder  $C_{1-4}$ -Alkyl oder Phenyl( $C_{1-4}$ -alkyl) und  $R^{15}$  gleich  $C_{1-4}$ -Alkyl bedeutet,  $CyB^1$  wie in Anspruch 1 für  $CyB$  definiert ist, wobei  $CyB^1$  an Z über ein Kohlenstoffatom in dem  $CyB^1$ -Ring gebunden ist, und die anderen Symbole wie in Anspruch 1 definiert sind, mit einer Verbindung der Formel:

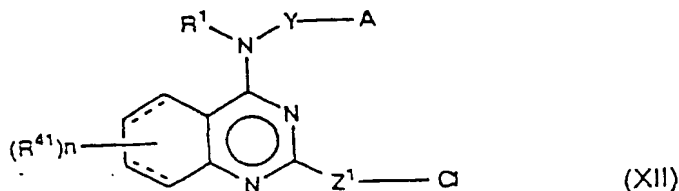
20



30 worin alle Symbole wie in Anspruch 1 definiert sind, zur Bildung einer Verbindung der Formel (IA):



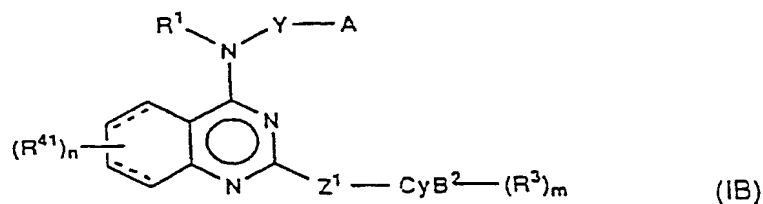
45 worin  $R^{41}$  und  $CyB^1$  wie oben definiert sind und die anderen Symbole wie in Anspruch 1 definiert sind;  
(b) Umsetzen einer Verbindung der Formel:



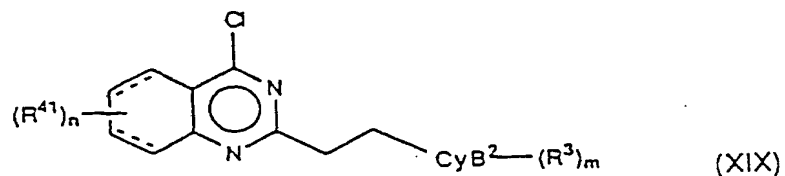
worin  $R^{41}$  wie oben definiert ist,  $Z^1$  eine Einfachbindung oder Methylen ist und die anderen Symbole wie in Anspruch 1 definiert sind, mit einer Verbindung der Formel:



worin  $\text{CyB}^2$  wie in Anspruch 1 für CyB definiert ist, wobei  $\text{CyB}^2$  an  $\text{Z}^1$  über ein Stickstoffatom in dem  $\text{CyB}^2$ -Ring gebunden ist, und die anderen Symbole wie in Anspruch 1 definiert sind, zur Bildung einer Verbindung der Formel (IB):



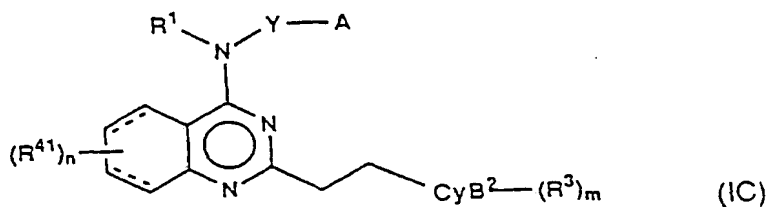
worin  $\text{R}^{41}$ ,  $\text{Z}$  und  $\text{CyB}^2$  wie oben definiert sind und die anderen Symbole wie in Anspruch 1 definiert sind; oder (c) Umsetzen einer Verbindung der Formel:



worin  $\text{R}^{41}$  und  $\text{CyB}^2$  wie oben definiert sind und die anderen Symbole wie in Anspruch 1 definiert sind, mit einer Verbindung der Formel:



worin alle Symbole wie in Anspruch 1 definiert sind, zur Bildung einer Verbindung der Formel (IC):



worin  $\text{R}^{41}$  und  $\text{CyB}^2$  wie oben definiert sind und die anderen Symbole wie in Anspruch 1 definiert sind; und optionales Umwandeln der auf diese Weise erhaltenen Verbindung der Formel (I) in eine andere Verbindung der Formel (I).

9. Pharmazeutische Zusammensetzung zur Behandlung von Säugetieren einschließlich Menschen, die als Wirkstoff eine wirksame Menge einer Verbindung der Formel (I), eines pharmazeutisch akzeptablen Salzes derselben oder

eines Hydrats derselben in Verbindung mit einem pharmazeutisch akzeptablen Träger oder Überzug umfasst.

10. Verbindung der Formel (I) gemäß Definition in Anspruch 1, ein pharmazeutisch akzeptables Salz derselben oder ein Hydrat derselben zur Verwendung als Medikament bei der Behandlung von Säugetieren.

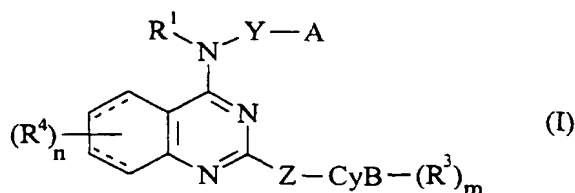
11. Verbindung gemäß Anspruch 1, die da ist:

- (1) 4-Phenylmethylamino-2-(3-pyridyl)chinazolin,
- (2) 4-(3-Methylphenylmethyl)amino-2-(3-pyridyl)chinazolin,
- (3) 4-(3,4-Dimethoxyphenylmethyl)amino-2-(3-pyridyl)-chinazolin,
- (4) 4-(4-Carboxyphenylmethyl)amino-2-(3-pyridyl)-chinazolin,
- (5) 4-(3-Chlorphenylmethyl)amino-2-(3-pyridyl)chinazolin,
- (6) 4-(3-Trifluormethylphenylmethyl)amino-2-(3-pyridyl)-chinazolin,
- (7) 4-(3-Nitrophenylmethyl)amino-2-(3-pyridyl)chinazolin,
- (8) 4-Phenylmethylamino-2-(6-chlor-3-pyridyl)chinazolin,
- (9) 4-Phenylmethylamino-6-methyl-2-(3-pyridyl)chinazolin,
- (10) 4-Phenylmethylamino-6,7-dimethoxy-2-(3-pyridyl)-chinazolin,
- (11) 4-Phenylmethylamino-6-acetylamino-2-(3-pyridyl)-chinazolin,
- (12) 4-Phenylmethylamino-6-chlor-2-(3-pyridyl)chinazolin,
- (13) 4-Phenylmethylamino-6-brom-2-(3-pyridyl)chinazolin,
- (14) 4-Phenylmethylamino-7-fluor-2-(3-pyridyl)chinazolin,
- (15) 4-Phenylmethylamino-6-nitro-2-(3-pyridyl)chinazolin,
- (16) 4-Phenylamino-2-(3-pyridyl)chinazolin,
- (17) 4-(3-Methoxycarbonylphenyl)amino-2-(3-pyridyl)-chinazolin,
- (18) 4-Phenylethylamino-2-(3-pyridyl)chinazolin,
- (19) 4-Phenylmethylamino-2-(2-pyridyl)chinazolin,
- (20) 4-Phenylmethylamino-2-(4-pyridyl)chinazolin,
- (21) 6-Iod-4-phenylmethylamino-2-(3-pyridyl)chinazolin,
- (22) 4-(3-Carboxyphenyl)amino-2-(4-pyridyl)chinazolin,
- (23) 6-Fluor-4-phenylmethylamino-2-(3-pyridyl)chinazolin,
- (24) 4-(Cyclopropylmethyl)amino-2-(3-pyridyl)chinazolin,
- (25) 4-(3-Pyridylmethyl)amino-2-(3-pyridyl)chinazolin,
- (26) 4-(2-Thienylmethyl)amino-2-(3-pyridyl)chinazolin,
- (27) 4-(2-Furylmethyl)amino-2-(1-imidazolyl)chinazolin,
- (28) 4-(2-Tetrahydrofuranylmethyl)amino-2-(1-imidazolyl)-chinazolin,
- (29) 4-(4-Tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-chinazolin,
- (30) 6-Methoxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)chinazolin,
- (31) 6-Chlor-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)chinazolin,
- (32) 4-(2-Thienylmethyl)amino-2-(1-imidazolyl)chinazolin,
- (33) 6-Acetyl-4-(2-methoxyethyl)amino-2-(3-pyridyl)-chinazolin,
- (34) 4-Phenylmethylamino-6-methoxy-2-(1-imidazolyl)-chinazolin,
- (35) 4-Phenylmethylamino-6,7-dimethoxy-2-(1-imidazolyl)-chinazolin,
- (36) 4-Phenylmethylamino-6-carboxy-2-(1-imidazolyl)-chinazolin,
- (37) 4-Phenylmethylamino-6-chlor-2-(1-imidazolyl)-chinazolin,
- (38) 4-Phenylmethylamino-6-brom-2-(1-imidazolyl)chinazolin,
- (39) 4-Phenylmethylamino-6-nitro-2-(1-imidazolyl)-chinazolin,
- (40) 4-Phenylmethylamino-2-(1-imidazolyl)chinazolin,
- (41) 4-Phenylmethylamino-2-(2-methyl-1-imidazolyl)-chinazolin,
- (42) 7-Chlor-4-phenylmethylamino-2-(1-imidazolyl)-chinazolin,
- (43) 4-(3,4-Dimethoxyphenylmethyl)amino-2-(1-imidazolyl)-chinazolin,
- (44) 4-(2-Phenylethyl)amino-2-(1-imidazolyl)chinazolin,
- (45) 4-Cyclohexylmethylamino-2-(1-imidazolyl)chinazolin,
- (46) 6-Iod-4-phenylmethylamino-2-(1-imidazolyl)chinazolin,
- (47) 4-Phenylmethylamino-2-(1-triazolyl)-chinazolin,
- (48) 4-Phenylmethylamino-6,8-diiod-2-(1-imidazolyl)-chinazolin,
- (49) 4-Phenylmethylamino-2-(2-thienyl)chinazolin,
- (50) 4-Phenylmethylamino-2-(2-furyl)chinazolin,
- (51) 4-Phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydrochinazolin,

- (52) 6-Carboxy-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydrochinazolin oder  
(53) 6-Ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydrochinazolin.

## 5 Revendications

### 1. Dérivé de quinazoline de formule:



dans laquelle

[1]..... représente une liaison simple ou double;

R¹ est un atome d'hydrogène ou un groupe alkyle en C<sub>1-4</sub>;

Y est un groupe alkylène en C<sub>1-6</sub>;

A est un groupe -O-R⁰ ou -S(O)<sub>p</sub>-R⁰, dans lesquels R⁰ est un groupe hydroxyalkyle en C<sub>1-4</sub>, p est compris entre 0 et 2;

Z est une simple liaison, un groupe méthylène, éthylène, vinylène ou éthylnylène;

CyB est

- (1) un groupe hétéroaryle à 4 à 7 chaînons contenant un atome d'azote,
- (2) un groupe hétéroaryle à 4 à 7 chaînons contenant deux atomes d'azote,
- (3) un groupe hétéroaryle à 4 à 7 chaînons contenant trois atomes d'azote,
- (4) un groupe hétéroaryle à 4 à 7 chaînons contenant un ou deux atomes d'oxygène,
- (5) un groupe hétéroaryle à 4 à 7 chaînons contenant un ou deux atomes de soufre,

R³ est un atome d'hydrogène, un groupe alkyle en C<sub>1-4</sub>, alcoxy en C<sub>1-4</sub>, halogène ou trifluorométhyle;  
R⁴ est (1) un atome d'hydrogène, (2) un groupe alkyle en C<sub>1-4</sub>, (3) un groupe alcoxy en C<sub>1-4</sub>, (4) un groupe -COOR⁸, dans lequel R⁸ est un atome d'hydrogène ou un groupe alkyle en C<sub>1-4</sub>, (5) un groupe -NR⁹R¹⁰, dans lequel R⁹ est un atome d'hydrogène, un groupe alkyle en C<sub>1-4</sub> ou phényl(alkyle en C<sub>1-4</sub>) et R¹⁰ est un atome d'hydrogène ou un groupe alkyle en C<sub>1-4</sub>, (6) un groupe -NHCOR¹¹, dans lequel R¹¹ est un groupe alkyle en C<sub>1-4</sub>, (7) un groupe -NHSO₂R¹¹, dans lequel R¹¹ est tel que défini précédemment, (8) un groupe -SO₂NR⁹R¹⁰, dans lequel R⁹ et R¹⁰ sont tels que définis précédemment, (9) un groupe -OCOR¹¹, dans lequel R¹¹ est tel que défini précédemment, (10) un atome d'halogène, (11) un groupe trifluorométhyle, (12) un groupe hydroxy, (13) un groupe nitro, (14) un groupe cyano, (15) un groupe -SO₂N=CHNR¹²R¹³, dans lequel R¹² est un atome d'hydrogène ou un groupe alkyle en C<sub>1-4</sub> et R¹³ est un groupe alkyle en C<sub>1-4</sub>, (16) un groupe -CONR¹⁴R¹⁵, dans lequel R¹⁴ est un atome d'hydrogène, un groupe alkyle en C<sub>1-4</sub> ou phényl(alkyle en C<sub>1-4</sub>) et R¹⁵ est un groupe alkyle en C<sub>1-4</sub>, (17) un groupe alkylthio en C<sub>1-4</sub>, (18) un groupe alkylsulfonyle en C<sub>1-4</sub>, (19) un groupe alkylsulfonyl en C<sub>1-4</sub>, (20) un groupe éthylnyle, (21) un groupe hydroxyméthyle, (22) un groupe tri(alkyl en C<sub>1-4</sub>)silyléthylnyle ou (23) un groupe acétyle;  
m et n sont indépendamment 1 ou 2;

[2]....., R¹, p, Z, CyB, R³, m, n sont tels que définis précédemment;

Y est une liaison ou un groupe alkylène en C<sub>1-6</sub>;

A est

- (i) un groupe -CyA-(R²)¹ ou
- (ii) un groupe -O-R⁰ ou -S(O)<sub>p</sub>-R⁰,

dans lesquels  $R^0$  est un atome d'hydrogène, un groupe alkyle en  $C_{1-4}$  ou  $-CyA-(R^2)_1$ ,  
CyA est

- (1) un carbocycle à 3 à 7 chaînons saturé ou insaturé,
- (2) un hétérocycle à 4 à 7 chaînons insaturé ou partiellement saturé contenant un atome d'azote,
- (3) un hétérocycle à 4 à 7 chaînons insaturé ou partiellement saturé contenant un atome d'azote et un atome d'oxygène,
- (4) un hétérocycle à 4 à 7 chaînons insaturé ou partiellement saturé contenant un atome d'azote et deux atomes d'oxygène,
- (5) un hétérocycle à 4 à 7 chaînons insaturé ou partiellement saturé contenant deux atomes d'azote et un atome d'oxygène,
- (6) un hétérocycle à 4 à 7 chaînons insaturé ou partiellement saturé contenant un ou deux atomes de soufre,
- (7) un hétérocycle à 4 à 7 chaînons insaturé, partiellement saturé ou totalement saturé contenant un ou deux atomes d'oxygène;

$R^2$  est (1) un atome d'hydrogène, (2) un groupe alkyle en  $C_{1-4}$ , (3) un groupe alcoxy en  $C_{1-4}$ , (4) un groupe  $-COOR^5$ , dans lequel  $R^5$  est un atome d'hydrogène ou un groupe alkyle en  $C_{1-4}$ , (5) un groupe  $-NR^6R^7$ , dans lequel  $R^6$  et  $R^7$  sont indépendamment un atome d'hydrogène ou un groupe alkyle en  $C_{1-4}$ , (6) un groupe  $-SO_2NR^6R^7$ , dans lequel  $R^6$  et  $R^7$  sont tels que définis précédemment, (7) un atome d'halogène, (8) un groupe trifluorométhyle, (9) un groupe nitro ou (10) un groupe trifluorométhoxy;

1 est 1 ou 2;

lorsque Z est un groupe méthylène, éthylène, vinylène ou éthylnylène,

$R^4$  est (1) un atome d'hydrogène, (2) un groupe alkyle en  $C_{1-4}$ , (3) un groupe alcoxy en  $C_{1-4}$ , (4) un groupe  $-COOR^8$ , dans lequel  $R^8$  est un atome d'hydrogène ou un groupe alkyle en  $C_{1-4}$ , (5) un groupe  $-NR^9R^{10}$ , dans lequel  $R^9$  est un atome d'hydrogène, un groupe alkyle en  $C_{1-4}$  ou phényl(alkyle en  $C_{1-4}$ ) et  $R^{10}$  est un atome d'hydrogène ou un groupe alkyle en  $C_{1-4}$ , (6) un groupe  $-NHCOR^{11}$ , dans lequel R est un groupe alkyle en  $C_{1-4}$ , (7) un groupe  $-NHSO_2R^{11}$ , dans lequel  $R^{11}$  est tel que défini précédemment, (8) un groupe  $-SO_2NR^9R^{10}$ , dans lequel  $R^9$  et  $R^{10}$  sont tels que définis précédemment, (9) un groupe  $-OCOR^{11}$ , dans lequel  $R^{11}$  est tel que défini précédemment, (10) un atome d'halogène, (11) un groupe trifluorométhyle, (12) un groupe hydroxy, (13) un groupe nitro, (14) un groupe cyano, (15) un groupe  $-SO_2N=CHNR^{12}R^{13}$ , dans lequel  $R^{12}$  est un atome d'hydrogène ou un groupe alkyle en  $C_{1-4}$  et  $R^{13}$  est un groupe alkyle en  $C_{1-4}$ , (16) un groupe  $-CONR^{14}R^{15}$ , dans lequel  $R^{14}$  est un atome d'hydrogène, un groupe alkyle en  $C_{1-4}$  ou phényl(alkyle en  $C_{1-4}$ ) et  $R^{15}$  est un groupe alkyle en  $C_{1-4}$ , (17) un groupe alkylthio en  $C_{1-4}$ , (18) un groupe alkylsulfinyle en  $C_{1-4}$ , (19) un groupe alkylsulfonyl en  $C_{1-4}$ , (20) un groupe éthylnyle, (21) un groupe hydroxyméthyle, (22) un groupe tri(alkyl en  $C_{1-4}$ )silyléthylnyle ou (23) un groupe acétyle;

lorsque Z est une liaison simple,

$R^4$  est (1) un groupe  $-NHSO_2R^{11}$ , dans lequel  $R^{11}$  est tel que défini précédemment, (2) un groupe  $-SO_2NR^9R^{10}$ , dans lequel  $R^9$  et  $R^{10}$  sont tels que définis précédemment, (3) un groupe  $-OCOR^{11}$ , dans lequel  $R^{11}$  est tel que défini précédemment, (4) un groupe hydroxy, (5) un groupe  $-SO_2N=CHNR^{12}R^{13}$ , dans lequel  $R^{12}$  et  $R^{13}$  sont tels que définis précédemment, (6) un groupe  $-CONR^{14}R^{15}$ , dans lequel  $R^{14}$  et  $R^{15}$  sont tels que définis précédemment, (7) un groupe éthylnyle ou (8) un groupe tri(alkyl en  $C_{1-4}$ )silyléthylnyle;

[3] ..... ,  $R^1$ , p, CyB,  $R^3$ , m, n, CyA et 1 sont tels que définis précédemment;

Y est une liaison ou un groupe alkylène en  $C_{1-6}$ ;

A est

(i) un groupe  $-CyA-(R^2)_1$ , dans lequel  $R^2$  est (1) un groupe  $-NR^6R^7$ , dans lequel  $R^6$  et  $R^7$  sont indépendamment un atome d'hydrogène ou un groupe alkyle en  $C_{1-4}$  (à condition que  $R^6$  et  $R^7$  ne soient pas en même temps un atome d'hydrogène), (2) un groupe  $-SO_2NR^6R^7$ , dans lequel  $R^6$  et  $R^7$  sont indépendamment un atome d'hydrogène ou un groupe alkyle en  $C_{1-4}$  ou (3) un groupe trifluorométhoxy; ou

(ii) un groupe  $-O-R^0$ , dans lequel  $R^0$  est un groupe  $-CyA-(R^2)_1$ ; ou un groupe  $-S(O)_p-R^0$ , dans lequel  $R^0$  est un atome d'hydrogène, un groupe alkyle en  $C_{1-4}$  ou  $-CyA-(R^2)_1$ ;

où  $R^2$  est (1) un atome d'hydrogène, (2) un groupe alkyle en  $C_{1-4}$ , (3) un groupe alcoxy en  $C_{1-4}$ , (4) un

groupe  $\text{-COOR}^5$ , dans lequel  $\text{R}^5$  est un atome d'hydrogène ou un groupe alkyle en  $\text{C}_{1-4}$ , (5) un groupe  $\text{-NR}^6\text{R}^7$ , dans lequel  $\text{R}^6$  et  $\text{R}^7$  sont indépendamment un atome d'hydrogène ou un groupe alkyle en  $\text{C}_{1-4}$ , (6) un groupe  $\text{-SO}_2\text{NR}^6\text{R}^7$ , dans lequel  $\text{R}^6$  et  $\text{R}^7$  sont tels que définis précédemment, (7) un atome d'halogène, (8) un groupe trifluorométhyle, (9) un groupe nitro ou (10) un groupe trifluorométhoxy;

Z est une liaison simple;

$\text{R}^4$  est (1) un atome d'hydrogène, (2) un groupe alkyle en  $\text{C}_{1-4}$ , (3) un groupe alcoxy en  $\text{C}_{1-4}$ , (4) un groupe  $\text{-COOR}^8$ , dans lequel  $\text{R}^8$  est un atome d'hydrogène ou un groupe alkyle en  $\text{C}_{1-4}$ , (5) un groupe  $\text{-NR}^9\text{R}^{10}$ , dans lequel  $\text{R}^9$  est un atome d'hydrogène, un groupe alkyle en  $\text{C}_{1-4}$  ou phényle (alkyle en  $\text{C}_{1-4}$ ) et  $\text{R}^{10}$  est un atome d'hydrogène ou un groupe alkyle en  $\text{C}_{1-4}$ , (6) un groupe  $\text{-NHCOR}^{11}$ , dans lequel  $\text{R}^{11}$  est un groupe alkyle en  $\text{C}_{1-4}$ , (7) un atome d'halogène, (8) un groupe trifluorométhyle, (9) un groupe nitro, (10) un groupe cyano, (11) un groupe alkylthio en  $\text{C}_{1-4}$ , (12) un groupe alkylsulfinyle en  $\text{C}_{1-4}$ , (13) un groupe alkylsulfonyl en  $\text{C}_{1-4}$ , (14) un groupe hydroxyméthyle ou (15) un groupe acétyle;

à la condition que

(1)  $\text{-CyA-(R}^2)_1$  ne représente pas un groupe cyclopentyle et trifluorométhylphényle, lorsque Y est une liaison simple;

(2) CyB ne soit pas lié à Z par l'intermédiaire d'un atome d'azote, lorsque Z est un groupe vinyène ou éthynylène;

(3) CyB ne soit pas un reste pyridine ou thiophène, lorsque CyA est un hétérocycle à 4 à 7 chaînons insaturé, partiellement saturé ou totalement saturé contenant un ou deux atomes d'oxygène;

(4) Y ne soit pas une liaison simple, lorsque A est (ii) un groupe  $\text{-O-R}^0$  ou  $\text{-S(O)}_p\text{-R}^0$ ;

ou un composé qui est :

- (1) la 4-phénylméthylamino-2-(3-pyridyl)quinazoline,
- (2) la 4-(3-méthylphénylméthyl)amino-2-(3-pyridyl)quinazoline,
- (3) la 4-(3,4-diméthoxyphénylméthyl)amino-2-(3-pyridyl)quinazoline,
- (4) la 4-(4-carboxyphénylméthyl)amino-2-(3-pyridyl)quinazoline,
- (5) la 4-(3-chlorophénylméthyl)amino-2-(3-pyridyl)quinazoline,
- (6) la 4-(3-trifluorométhylphénylméthyl)amino-2-(3-pyridyl)quinazoline,
- (7) la 4-(3-nitrophénylméthyl)amino-2-(3-pyridyl)quinazoline,
- (8) la 4-phénylméthylamino-2-(6-chloro-3-pyridyl)quinazoline,
- (9) la 4-phénylméthylamino-6-méthyl-2-(3-pyridyl)quinazoline,
- (10) la 4-phénylméthylamino-6,7-diméthoxy-2-(3-pyridyl)quinazoline,
- (11) la 4-phénylméthylamino-6-acétylamino-2-(3-pyridyl)quinazoline,
- (12) la 4-phénylméthylamino-6-chloro-2-(3-pyridyl)quinazoline,
- (13) la 4-phénylméthylamino-6-bromo-2-(3-pyridyl)quinazoline,
- (14) la 4-phénylméthylamino-7-fluoro-2-(3-pyridyl)quinazoline,
- (15) la 4-phénylméthylamino-6-nitro-2-(3-pyridyl)quinazoline,
- (16) la 4-phénylamino-2-(3-pyridyl)quinazoline,
- (17) la 4-(3-méthoxycarbonylphényl)amino-2-(3-pyridyl)quinazoline,
- (18) la 4-phényléthylamino-2-(3-pyridyl)quinazoline,
- (19) la 4-phénylméthylamino-2-(2-pyridyl)quinazoline,
- (20) la 4-phénylméthylamino-2-(4-pyridyl)quinazoline,
- (21) la 6-iodo-4-phénylméthylamino-2-(3-pyridyl)quinazoline,
- (22) la 4-(3-carboxyphényl)amino-2-(4-pyridyl)quinazoline,
- (23) la 6-fluoro-4-phénylméthylamino-2-(3-pyridyl)quinazoline,
- (24) la 4-(cyclopropylméthyl)amino-2-(3-pyridyl)quinazoline,
- (25) la 4-(3-pyridylméthyl)amino-2-(3-pyridyl)quinazoline,
- (26) la 4-(2-thiénylméthyl)amino-2-(3-pyridyl)quinazoline,
- (27) la 4-(2-furylméthyl)amino-2-(1-imidazolyl)quinazoline,
- (28) la 4-(2-tétrahydrofuranylméthyl)amino-2-(1-imidazolyl)quinazoline,
- (29) la 4-(4-tétrahydropyranylméthyl)amino-2-(1-imidazolyl)quinazoline,
- (30) la 6-méthoxy-4-(4-tétrahydropyranylméthyl)amino-2-(1-imidazolyl)quinazoline,
- (31) la 6-chloro-4-(4-tétrahydropyranylméthyl)amino-2-(1-imidazolyl)quinazoline,
- (32) la 4-(2-thiénylméthyl)amino-2-(1-imidazolyl)quinazoline,
- (33) la 6-acétyl-4-(2-méthoxyéthyl)amino-2-(3-pyridyl)quinazoline,
- (34) la 4-phénylméthylamino-6-méthoxy-2-(1-imidazolyl)quinazoline,



- (35) la 4-phénylméthylamino-6,7-diméthoxy-2-(1-imidazolyl)quinazoline,  
 (36) la 4-phénylméthylamino-6-carboxy-2-(1-imidazolyl)quinazoline,  
 (37) la 4-phénylméthylamino-6-chloro-2-(1-imidazolyl)quinazoline,  
 (38) la 4-phénylméthylamino-6-bromo-2-(1-imidazolyl)quinazoline,  
 (39) la 4-phénylméthylamino-6-nitro-2-(1-imidazolyl)quinazoline,  
 (40) la 4-phénylméthylamino-2-(1-imidazolyl)quinazoline,  
 (41) la 4-phénylméthylamino-2-(2-méthyl-1-imidazolyl)quinazoline,  
 (42) la 7-chloro-4-phénylméthylamino-2-(1-imidazolyl)quinazoline,  
 (43) la 4-(3,4-diméthoxyphénylméthyl)amino-2-(1-imidazolyl)quinazoline,  
 (44) la 4-(2-phényléthyl)amino-2-(1-imidazolyl)quinazoline,  
 (45) la 4-cyclohexylméthylamino-2-(1-imidazolyl)quinazoline,  
 (46) la 6-iodo-4-phénylméthylamino-2-(1-imidazolyl)quinazoline,  
 (47) la 4-phénylméthylamino-2-(1-triazolyl)quinazoline,  
 (48) la 4-phénylméthylamino-6,8-diiodo-2-(1-imidazolyl)quinazoline,  
 (49) la 4-phénylméthylamino-2-(2-thiényl)quinazoline,  
 (50) la 4-phénylméthylamino-2-(2-furyl)quinazoline,  
 (51) la 4-phénylméthylamino-2-(1-imidazolyl)-5,6,7,8-tétrahydroquinazoline,  
 (52) la 6-carboxy-4-phénylméthylamino-2-(1-imidazolyl)-5,6,7,8-tétrahydroquinazoline ou  
 (53) la 6-éthoxycarbonyl-4-phénylméthylamino-2-(1-imidazolyl)-5,6,7,8-tétrahydroquinazoline;

ou un de ses sels pharmaceutiquement acceptables ou un de ses hydrates.

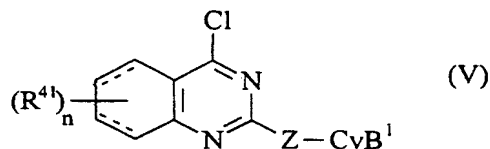
2. Composé selon la revendication 1, dans lequel CyB est un cycle pyridine, un cycle imidazole, un cycle triazole ou pyrrole ou un cycle furanne ou thiophène.  
 3. Composé selon la revendication 1 ou 2, dans lequel CyA est un cycle benzénique, un cycle cyclopropyle, un cycle cyclohexyle, un cycle pyridine, un cycle pyrrole ou isoxazole, un cycle thiophène ou un cycle furanne, tétrahydrofuranne ou pyrane.  
 4. Composé selon la revendication 1 ou 2, dans lequel A est un groupe OH, -O-(alkyle en C<sub>1-4</sub>), -O-(alkyl en C<sub>1-4</sub>)-OH ou -S(O)<sub>p</sub>-(alkyle en C<sub>1-4</sub>).  
 5. Composé selon l'une quelconque des revendications 1 à 4, dans lequel Y est une simple liaison, un groupe méthylène ou éthylène.  
 6. Composé selon l'une quelconque des revendications 1 à 5, dans lequel Z est une liaison simple, un groupe méthylène et vinyène.  
 7. Composé selon l'une quelconque des revendications précédentes, qui est:

- (1) la 4-(4-(N,N-diméthylamino)phénylméthyl)amino-2-(3-pyridyl)quinazoline,  
 (2) la 4-(4-sulfamoylphénylméthyl)amino-2-(3-pyridyl)quinazoline,  
 (3) la 4-phénylméthylamino-2-(2-(3-pyridyl)viny)quinazoline,  
 (4) la 4-(2-phénoxyéthyl)amino-2-(1-imidazolyl)quinazoline,  
 (5) la 6-chloro-4-(2-(2-hydroxyéthoxy)éthyl)amino-2-(1-imidazolyl)quinazoline,  
 (6) la 6-méthoxy-4-(2-(2-hydroxyéthoxy)éthyl)amino-2-(1-imidazolyl)quinazoline,  
 (7) la 4-(2-(2-hydroxyéthoxy)éthyl)amino-6-iodo-2-(1-imidazolyl)quinazoline,  
 (8) la 4-(2-(2-hydroxyéthoxy)éthyl)amino-6-méthylsulfinyl-2-(1-imidazolyl)-quinazoline,  
 (9) la 2-(1-imidazolyl)-4-(2-méthoxyéthyl)amino-6-(2-triéthylsilyléthynyl)-quinazoline,  
 (10) la 6-éthynyl-4-(2-méthoxyéthyl)amino-2-(3-pyridyl)quinazoline,  
 (11) la 4-[2-(2-hydroxyéthoxy)éthyl]amino-6-acétyl-2-(1-imidazolyl)quinazoline,  
 (12) la 4-(2-méthylthioéthyl)amino-6-méthoxy-2-(1-imidazolyl)quinazoline,  
 (13) la 4-(2-méthylsulfinyléthyl)amino-6-méthoxy-2-(1-imidazolyl)quinazoline,  
 (14) la 4-(2-méthylsulfonyléthyl)amino-6-méthoxy-2-(1-imidazolyl)quinazoline,  
 (15) la 4-[2-(2-hydroxyéthoxy)éthyl]amino-6-méthoxycarbonyl-2-(1-imidazolyl)-quinazoline,  
 (16) la 4-[2-(2-hydroxyéthoxy)éthyl]amino-6-hydroxyméthyl-2-(1-imidazolyl)-quinazoline,  
 (17) la 4-(2-(2-hydroxyéthoxy)éthyl)amino-6-méthylthio-2-(1-imidazolyl)-quinazoline,  
 (18) la 2-(1-imidazolyl)-4-[2-(2-hydroxyéthoxy)éthyl]amino-6-(2-triisopropylsilyléthynyl)quinazoline,

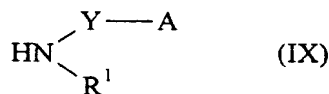
- (19) la 2-(1-imidazolyl)-4-[2-(2-hydroxyéthoxy)éthyl]amino-6-éthynylquinazoline,  
 (20) la 4-phénylméthylamino-6-hydroxy-2-(1-imidazolyl)quinazoline,  
 (21) la 4-phénylméthylamino-2-((1-imidazolyl)méthyl)quinazoline,  
 (22) la 6-chloro-4-phénylamino-2-(1-imidazolylméthyl)quinazoline,  
 (23) la 6-chloro-4-phénylméthylamino-2-(1-imidazolylméthyl)quinazoline,  
 (24) la 6-chloro-4-(3-carboxyphényl)amino-2-(1-imidazolylméthyl)quinazoline,  
 (25) la 6-diméthylaminosulfonyl-4-phénylméthylamino-2-(1-imidazolyl)quinazoline,  
 (26) la 6-diméthylaminométhylidèneaminosulfonyl-4-phénylméthylamino-2-(1-imidazolyl)quinazoline,  
 (27) la 6-(phénylméthylaminosulfonyl)-4-phénylméthylamino-2-(1-imidazolyl)quinazoline,  
 (28) la 4-(4-trifluorométhoxyphénylméthyl)amino-2-(1-imidazolyl)quinazoline,  
 (29) la 4-(3-trifluorométhoxyphénylméthyl)amino-2-(1-imidazolyl)quinazoline,  
 (30) la 4-(2-phénoxyéthyl)amino-6-méthoxy-2-(1-imidazolyl)quinazoline,  
 (31) la 6-éthylaminocarbonyl-4-phénylméthylamino-2-(1-imidazolyl)-5,6,7,8-tétrahydroquinazoline ou  
 (32) la 4-(2-(2-hydroxyéthoxy)éthyl)amino-2-(1-imidazolyl)-5,6,7,8-tétrahydroquinazoline.

8. Procédé pour la préparation d'un dérivé de 4-aminoquinazoline de formule (I) telle que définie dans la revendication 1, comprenant:

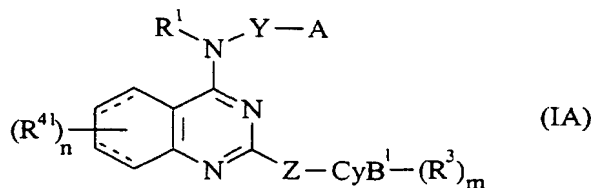
(a) la réaction d'un composé de formule:



dans laquelle R<sup>41</sup> est (1) un atome d'hydrogène, (2) un groupe alkyle en C<sub>1-4</sub>, (3) un groupe alcoxy en C<sub>1-4</sub>,  
 (4) un groupe -COOR<sup>8</sup>, dans lequel R<sup>8</sup> est un atome d'hydrogène ou un groupe alkyle en C<sub>1-4</sub>, (5) un groupe  
 -NR<sup>9</sup>R<sup>10</sup>, dans lequel R<sup>9</sup> et R<sup>10</sup> sont tels que définis précédemment, à condition que R<sup>9</sup> et R<sup>10</sup> ne soient pas  
 tous les deux un atome d'hydrogène, (6) un groupe -SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, dans lequel R<sup>9</sup> et R<sup>10</sup> sont tels que définis  
 précédemment, (7) un atome d'halogène, (8) un groupe trifluorométhyle, (9) un groupe nitro, (10) un groupe  
 cyano, (11) un groupe alkylthio en C<sub>1-4</sub>, (12) un groupe tri(alkyl en C<sub>1-4</sub>)silyléthynyle, (13) un groupe -  
 SO<sub>2</sub>N=CHNR<sup>12</sup>R<sup>13</sup>, dans lequel R<sup>12</sup> est un atome d'hydrogène ou un groupe alkyle en C<sub>1-4</sub> et R<sup>13</sup> est un  
 groupe alkyle en C<sub>1-4</sub> ou (14) un groupe -CONR<sup>14</sup>R<sup>15</sup>, dans lequel R<sup>14</sup> est un atome d'hydrogène ou un groupe  
 alkyle en C<sub>1-4</sub> ou phényl(alkyle en C<sub>1-4</sub>) et R<sup>15</sup> est un groupe alkyle en C<sub>1-4</sub>, CyB<sup>1</sup> est tel que défini dans la  
 revendication 1 pour CyB, à condition que CyB<sup>1</sup> soit lié à Z par l'intermédiaire d'un atome de carbone dans le  
 cycle CyB<sup>1</sup>, et les autres symboles sont tels que définis dans la revendication 1, avec un composé de formule:



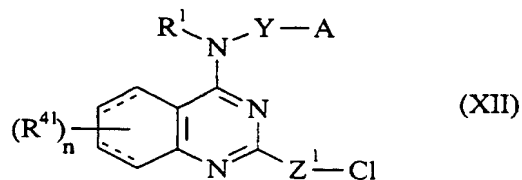
dans laquelle tous les symboles sont tels que définis dans la revendication 1, pour donner un composé de  
 formule (IA):



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dans laquelle  $R^{41}$  et  $CyB^1$  sont tels que définis ci-dessus et les autres symboles sont tels que définis dans la revendication 1;

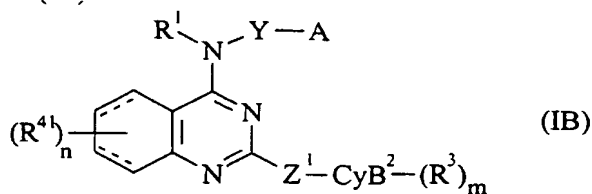
(b) la réaction d'un composé de formule:



dans laquelle  $R^{41}$  est tel que défini ci-dessus,  $Z^1$  est une liaison simple ou un groupe méthylène et les autres symboles sont tels que définis dans la revendication 1, avec un composé de formule:

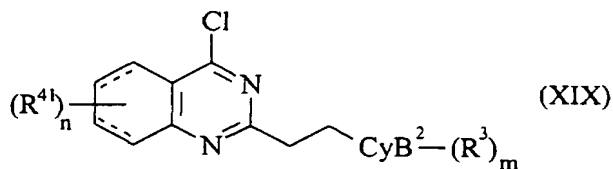


dans laquelle  $CyB^2$  est tel que défini dans la revendication 1 pour  $CyB$ , à condition que  $CyB^2$  soit lié à  $Z^1$  par l'intermédiaire d'un atome d'azote dans le cycle  $CyB^2$  et les autres symboles sont tels que définis dans la revendication 1, pour donner un composé de formule (IB):

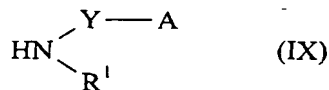


dans laquelle  $R^{41}$ ,  $Z$  et  $CyB^2$  sont tels que définis ci-dessus et les autres symboles sont tels que définis dans la revendication 1; ou

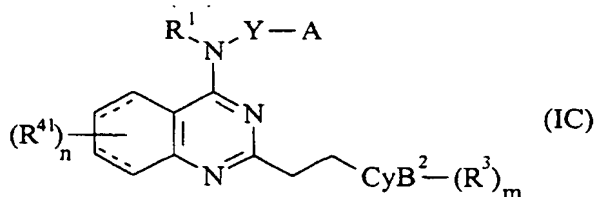
(c) la réaction d'un composé de formule:



dans laquelle  $R^{41}$  et  $CyB^2$  sont tels que définis ci-dessus et les autres symboles sont tels que définis dans la revendication 1 avec un composé de formule:



dans laquelle tous les symboles sont tels que définis dans la revendication 1, pour donner un composé de formule (IC):



10 dans laquelle R<sup>41</sup> et CyB<sup>2</sup> sont tels que définis ci-dessus et les autres symboles sont tels que définis dans la revendication 1; et

éventuellement la conversion du composé de formule (I) ainsi obtenu en un autre composé de formule (I).

15 9. Composition pharmaceutique pour le traitement des mammifères, y compris les êtres humains, comprenant en tant qu'ingrédient actif, une quantité efficace d'un composé de formule (I), un de ses sels pharmaceutiquement acceptables ou un de ses hydrates en association avec un excipient ou un enrobage pharmaceutiquement acceptable.

20 10. Composé de formule (I) tel que défini dans la revendication 1, un de ses sels pharmaceutiquement acceptables ou un de ses hydrates pour une utilisation en tant que médicament pour le traitement des mammifères.

11. Composé selon la revendication 1 qui est:

- 25 (1) la 4-phénylméthylamino-2-(3-pyridyl)quinazoline,  
 (2) la 4-(3-méthylphénylméthyl)amino-2-(3-pyridyl)quinazoline,  
 (3) la 4-(3,4-diméthoxyphénylméthyl)amino-2-(3-pyridyl)quinazoline,  
 (4) la 4-(4-carboxyphénylméthyl)amino-2-(3-pyridyl)quinazoline,  
 (5) la 4-(3-chlorophénylméthyl)amino-2-(3-pyridyl)quinazoline,  
 30 (6) la 4-(3-trifluorométhylphénylméthyl)amino-2-(3-pyridyl)quinazoline,  
 (7) la 4-(3-nitrophénylméthyl)amino-2-(3-pyridyl)quinazoline,  
 (8) la 4-phénylméthylamino-2-(6-chloro-3-pyridyl)quinazoline,  
 (9) la 4-phénylméthylamino-6-méthyl-2-(3-pyridyl)quinazoline,  
 (10) la 4-phénylméthylamino-6,7-diméthoxy-2-(3-pyridyl)quinazoline,  
 35 (11) la 4-phénylméthylamino-6-acétylamino-2-(3-pyridyl)quinazoline,  
 (12) la 4-phénylméthylamino-6-chloro-2-(3-pyridyl)quinazoline,  
 (13) la 4-phénylméthylamino-6-bromo-2-(3-pyridyl)quinazoline,  
 (14) la 4-phénylméthylamino-7-fluoro-2-(3-pyridyl)quinazoline,  
 (15) la 4-phénylméthylamino-6-nitro-2-(3-pyridyl)quinazoline,  
 40 (16) la 4-phénylamino-2-(3-pyridyl)quinazoline,  
 (17) la 4-(3-méthoxycarbonylphényl)amino-2-(3-pyridyl)quinazoline,  
 (18) la 4-phényléthylamino-2-(3-pyridyl)quinazoline,  
 (19) la 4-phénylméthylamino-2-(2-pyridyl)quinazoline,  
 (20) la 4-phénylméthylamino-2-(4-pyridyl)quinazoline,  
 45 (21) la 6-iodo-4-phénylméthylamino-2-(3-pyridyl)quinazoline,  
 (22) la 4-(3-carboxyphényl)amino-2-(4-pyridyl)quinazoline,  
 (23) la 6-fluoro-4-phénylméthylamino-2-(3-pyridyl)quinazoline,  
 (24) la 4-(cyclopropylméthyl)amino-2-(3-pyridyl)quinazoline,  
 (25) la 4-(3-pyridylméthyl)amino-2-(3-pyridyl)quinazoline,  
 50 (26) la 4-(2-thiénylméthyl)amino-2-(3-pyridyl)quinazoline,  
 (27) la 4-(2-furylméthyl)amino-2-(1-imidazolyl)quinazoline,  
 (28) la 4-(2-tétrahydrofurylméthyl)amino-2-(1-imidazolyl)quinazoline,  
 (29) la 4-(4-tétrahydropyranylméthyl)amino-2-(1-imidazolyl)quinazoline,  
 (30) la 6-méthoxy-4-(4-tétrahydropyranylméthyl)amino-2-(1-imidazolyl)quinazoline,  
 55 (31) la 6-chloro-4-(4-tétrahydropyranylméthyl)amino-2-(1-imidazolyl)quinazoline,  
 (32) la 4-(2-thiénylméthyl)amino-2-(1-imidazolyl)quinazoline,  
 (33) la 6-acétyl-4-(2-méthoxyéthyl)amino-2-(3-pyridyl)quinazoline,  
 (34) la 4-phénylméthylamino-6-méthoxy-2-(1-imidazolyl)quinazoline,

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- (35) la 4-phénylméthylamino-6,7-diméthoxy-2-(1-imidazolyl)quinazoline,  
(36) la 4-phénylméthylamino-6-carboxy-2-(1-imidazolyl)quinazoline,  
(37) la 4-phénylméthylamino-6-chloro-2-(1-imidazolyl)quinazoline,  
(38) la 4-phénylméthylamino-6-bromo-2-(1-imidazolyl)quinazoline,  
5 (39) la 4-phénylméthylamino-6-nitro-2-(1-imidazolyl)quinazoline,  
(40) la 4-phénylméthylamino-2-(1-imidazolyl)quinazoline,  
(41) la 4-phénylméthylamino-2-(2-méthyl-1-imidazolyl)quinazoline,  
(42) la 7-chloro-4-phénylméthylamino-2-(1-imidazolyl)quinazoline,  
(43) la 4-(3,4-diméthoxyphénylméthyl)amino-2-(1-imidazolyl)quinazoline,  
10 (44) la 4-(2-phényléthyl)amino-2-(1-imidazolyl)quinazoline,  
(45) la 4-cyclohexylméthylamino-2-(1-imidazolyl)quinazoline,  
(46) la 6-iodo-4-phénylméthylamino-2-(1-imidazolyl)quinazoline,  
(47) la 4-phénylméthylamino-2-(1-triazolyl)quinazoline,  
(48) la 4-phénylméthylamino-6,8-diiodo-2-(1-imidazolyl)quinazoline,  
15 (49) la 4-phénylméthylamino-2-(2-thiényl)quinazoline,  
(50) la 4-phénylméthylamino-2-(2-furyl)quinazoline,  
(51) la 4-phénylméthylamino-2-(1-imidazolyl)-5,6,7,8-tétrahydroquinazoline,  
(52) la 6-carboxy-4-phénylméthylamino-2-(1-imidazolyl)-5,6,7,8-tétrahydroquinazoline ou  
20 (53) la 6-éthoxycarbonyl-4-phénylméthylamino-2-(1-imidazolyl)-5,6,7,8-tétrahydroquinazoline.